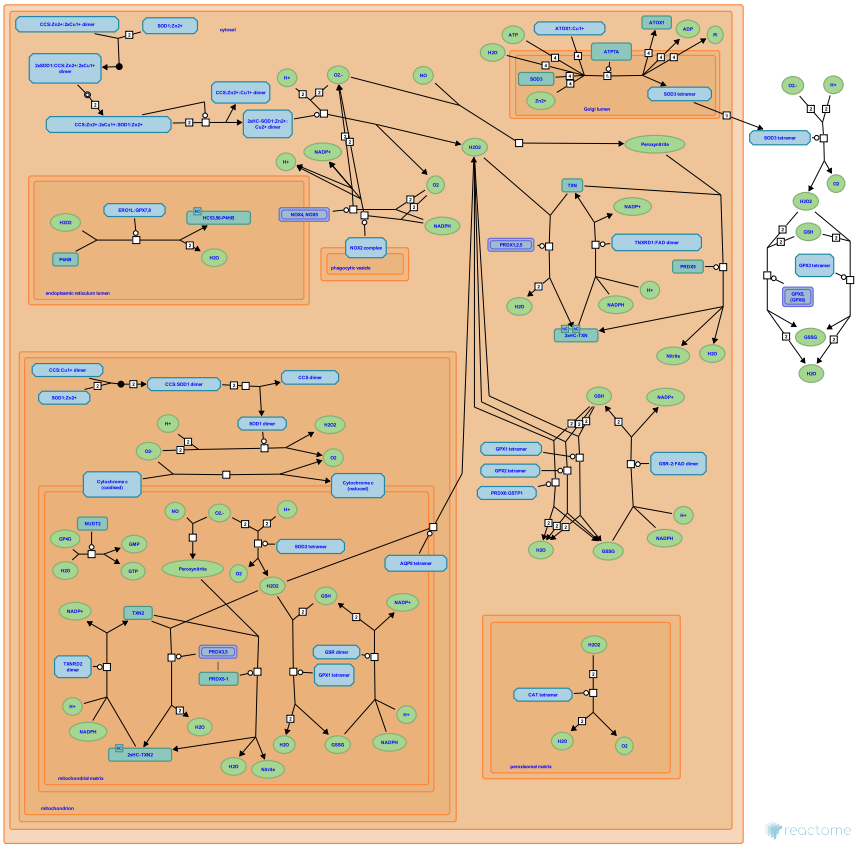
Detoxification of Reactive Oxygen Species



D'Eustachio, P., Inga, A., Jassal, B., Jupe, S., Kavdia, M., May, B., Stephan, R., Vastrik, I., Warner, D., Zaccara, S.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

12/11/2019

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

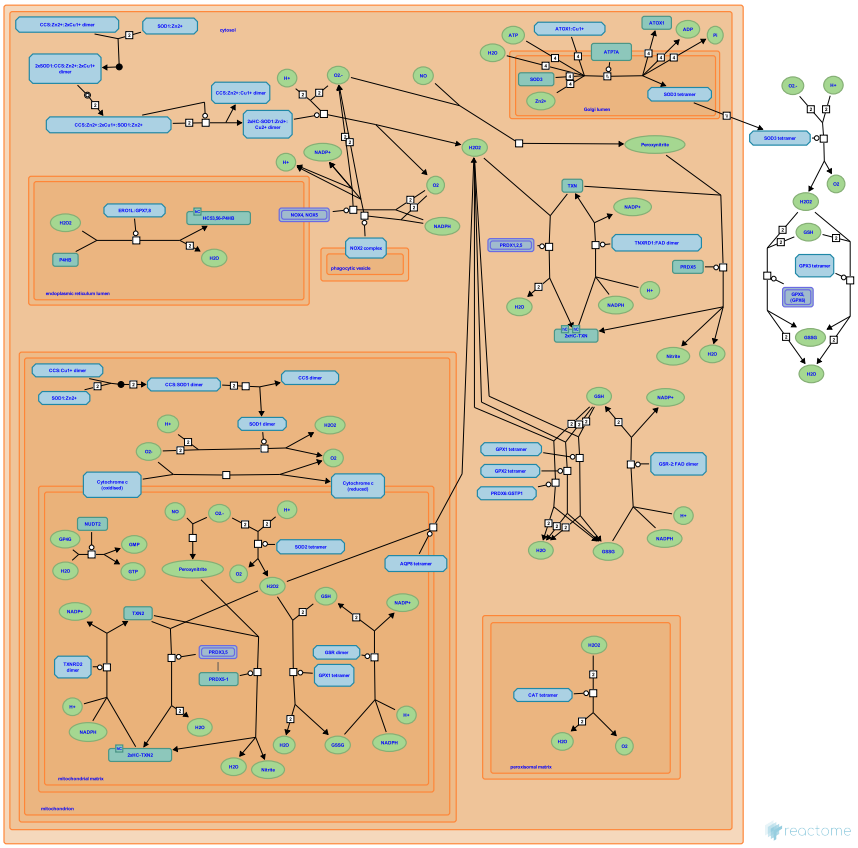
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Detoxification of Reactive Oxygen Species ↗

Stable identifier: R-HSA-3299685

Compartments: cytosol, endoplasmic reticulum lumen, extracellular region, mitochondrial inner membrane, mitochondrial intermembrane space, mitochondrial matrix, peroxisomal matrix



Reactive oxygen species such as superoxide (O2.-), peroxides (ROOR), singlet oxygen, peroxynitrite (ONOO-), and hydroxyl radical (OH.) are generated by cellular processes such as respiration (reviewed in Murphy 2009, Brand 2010) and redox enzymes and are required for signaling yet they are damaging due to their high reactivity (reviewed in Imlay 2008, Buettner 2011, Kavdia 2011, Birben et al. 2012, Ray et al. 2012). Aerobic cells have defenses that detoxify reactive oxygen species by converting them to less reactive products. Superoxide dismutases convert superoxide to hydrogen peroxide and oxygen (reviewed in Fukai and Ushio-Fukai 2011). Catalase and peroxidases then convert hydrogen peroxide to water.

Humans contain 3 superoxide dismutases: SOD1 is located in the cytosol and mitochondrial intermembrane space, SOD2 is located in the mitochondrial matrix, and SOD3 is located in the extracellular region. Superoxide, a negative ion, is unable to easily cross membranes and tends to remain in the compartment where it was produced. Hydrogen peroxide, one of the products of superoxide dismutase, is able to diffuse across membranes and pass through aquaporin channels. In most cells the primary source of hydrogen peroxide is mitochondria and, once in the cytosol, hydrogen peroxide serves as a signaling molecule to regulate redox-sensitive proteins such as transcription factors, kinases, phosphatases, ion channels, and others (reviewed in Veal and Day 2011, Ray et al. 2012). Hydrogen peroxide is decomposed to water by catalase, decomposed to water plus oxidized thioredoxin by peroxiredoxins, and decomposed to water plus oxidized glutathione by glutathione peroxidases (Presnell et al. 2013).

Literature references

Brand, MD. (2010). The sites and topology of mitochondrial superoxide production. *Exp. Gerontol., 45*, 466-72. ↗

Birben, E., Sahiner, UM., Sackesen, C., Erzurum, S., Kalayci, O. (2012). Oxidative stress and antioxidant defense. *World Allergy Organ J, 5*, 9-19.

Ray, PD., Huang, BW., Tsuji, Y. (2012). Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. *Cell. Signal., 24*, 981-90.

Murphy, MP. (2009). How mitochondria produce reactive oxygen species. *Biochem. J., 417*, 1-13.

Veal, E., Day, A. (2011). Hydrogen peroxide as a signaling molecule. *Antioxid. Redox Signal., 15*, 147-51.

Editions

2013-04-20	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

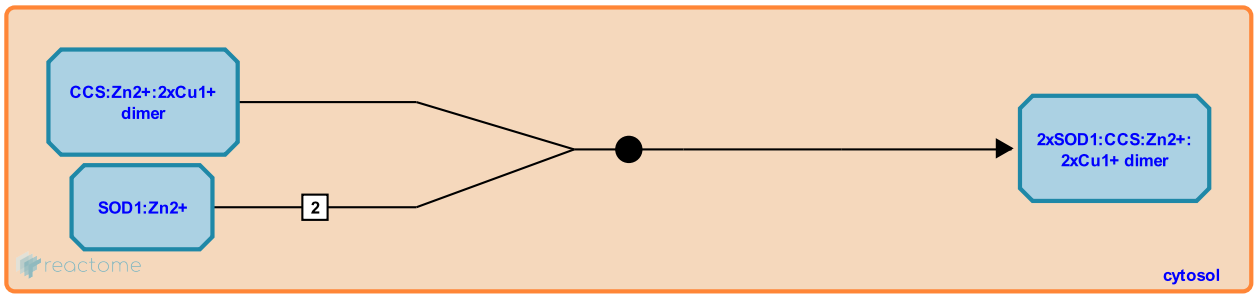
SOD1:Zn2+ apoenzyme binds CCS:Zn2+:2xCu1+

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3697860

Type: binding

Compartments: cytosol



Copper chaperone of superoxide dismutase (CCS) transfers a copper(I) atom to a SOD1 monomer that already contains a Zn atom (Culotta et al. 1997, Casareno et al. 1998, Rae et al. 2001, Brown et al. 2004, Banci et al. 2012). The reaction proceeds by a two step mechanism in which SOD1 first forms heterodimers with CCS (Rae et al. 2001, Banci et al. 2012).

Followed by: 2xSOD1:CCS:Zn2+:2xCu1+ dimer dissociates

Literature references

Banci, L., Bertini, I., Cantini, F., Kozyreva, T., Massagni, C., Palumaa, P. et al. (2012). Human superoxide dismutase 1 (hSOD1) maturation through interaction with human copper chaperone for SOD1 (hCCS). *Proc. Natl. Acad. Sci. U.S.A., 109*, 13555-60.

Casareno, RL., Waggoner, D., Gitlin, JD. (1998). The copper chaperone CCS directly interacts with copper/zinc superoxide dismutase. *J. Biol. Chem., 273*, 23625-8.

Culotta, VC., Klomp, LW., Strain, J., Casareno, RL., Krems, B., Gitlin, JD. (1997). The copper chaperone for superoxide dismutase. *J. Biol. Chem., 272*, 23469-72.

Kawamata, H., Manfredi, G. (2008). Different regulation of wild-type and mutant Cu,Zn superoxide dismutase localization in mammalian mitochondria. *Hum. Mol. Genet., 17*, 3303-17.

Rae, TD., Torres, AS., Pufahl, RA., O'Halloran, TV. (2001). Mechanism of Cu,Zn-superoxide dismutase activation by the human metallochaperone hCCS. *J. Biol. Chem., 276*, 5166-76.

Editions

2013-06-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

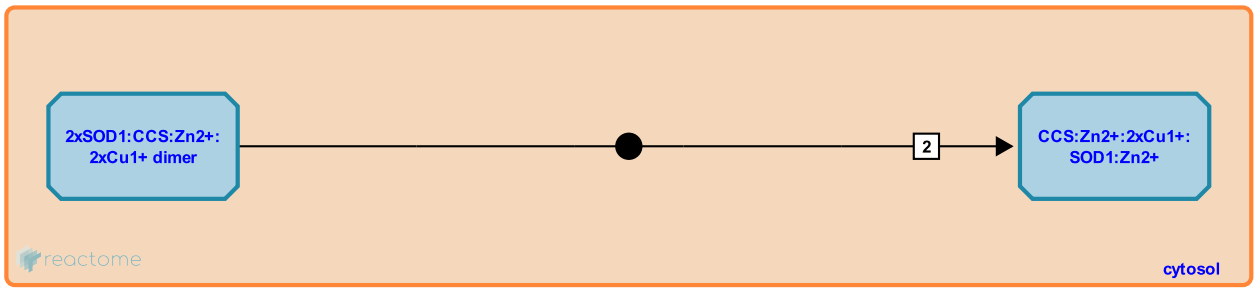
2xSOD1:CCS:Zn2+:2xCu1+ dimer dissociates ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-8951723

Type: dissociation

Compartments: cytosol



Copper chaperone of superoxide dismutase (CCS) transfers a copper(I) atom to a SOD1 monomer that already contains a Zn atom (Culotta et al. 1997, Casareno et al. 1998, Rae et al. 2001, Brown et al. 2004, Banci et al. 2012). The reaction proceeds by a two step mechanism in which SOD1 first forms heterodimers with CCS (Rae et al. 2001, Banci et al. 2012).

Preceded by: SOD1:Zn2+ apoenzyme binds CCS:Zn2+:2xCu1+

Followed by: CCS transfers Cu to SOD1 and oxidizes cysteine residues in SOD1

Literature references

Banci, L., Bertini, I., Cantini, F., Kozyreva, T., Massagni, C., Palumaa, P. et al. (2012). Human superoxide dismutase 1 (hSOD1) maturation through interaction with human copper chaperone for SOD1 (hCCS). *Proc. Natl. Acad. Sci. U.S.A., 109*, 13555-60. ↗

Casareno, RL., Waggoner, D., Gitlin, JD. (1998). The copper chaperone CCS directly interacts with copper/zinc superoxide dismutase. *J. Biol. Chem., 273*, 23625-8. ↗

Culotta, VC., Klomp, LW., Strain, J., Casareno, RL., Krems, B., Gitlin, JD. (1997). The copper chaperone for superoxide dismutase. *J. Biol. Chem., 272*, 23469-72. ↗

Kawamata, H., Manfredi, G. (2008). Different regulation of wild-type and mutant Cu,Zn superoxide dismutase localization in mammalian mitochondria. *Hum. Mol. Genet., 17*, 3303-17. ↗

Rae, TD., Torres, AS., Pufahl, RA., O'Halloran, TV. (2001). Mechanism of Cu,Zn-superoxide dismutase activation by the human metallochaperone hCCS. *J. Biol. Chem., 276*, 5166-76. ↗

Editions

2013-06-09	Authored	May, B.
2013-11-01	Reviewed	Kavdia, M.
2016-12-08	Edited	Jupe, S.

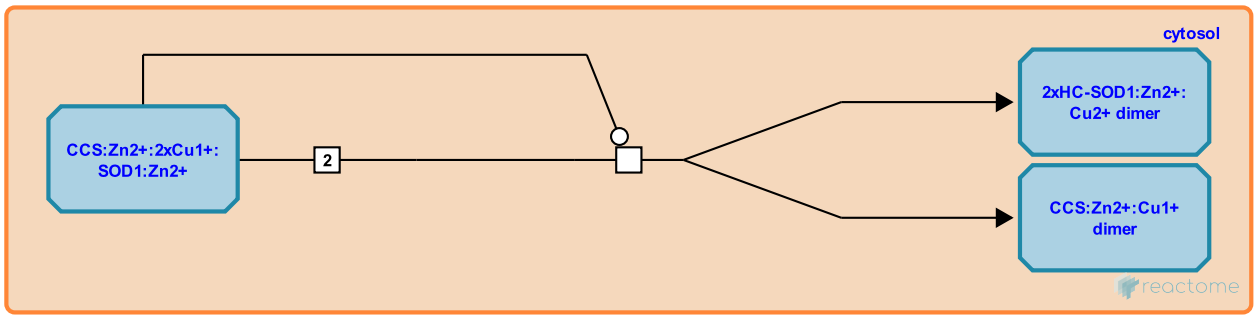
CCS transfers Cu to SOD1 and oxidizes cysteine residues in SOD1 ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3299753

Type: transition

Compartments: cytosol



Copper chaperone of superoxide dismutase (CCS) transfers a copper(I) atom to a SOD1 monomer that already contains a Zn atom. After initial heterodimerization between SOD1 and CCS, the copper atom is transferred, intramolecular cysteine disulfide bonds are formed in SOD1, and SOD1 dimerizes (Banci et al. 2012, Casareno et al. 1998, Culotta et al. 1997, Rae et al. 2001, Brown et al. 2004, Carroll et al. 2006, Kawamata and Manfredi 2008). The transfer of copper to SOD1 requires oxygen but it is unknown at which step the oxygen acts (Brown et al. 2004). There is also a CCS-independent, oxygen-independent pathway of maturation of SOD1 (Leitch et al. 2009) whose molecular details and physiological role are not well characterized.

Preceded by: 2xSOD1:CCS:Zn2+:2xCu1+ dimer dissociates

Followed by: SOD1 catalyzes 2H+ + 2O2.- => O2 + H2O2 (cytosol)

Literature references

Banci, L., Bertini, I., Cantini, F., Kozyreva, T., Massagni, C., Palumaa, P. et al. (2012). Human superoxide dismutase 1 (hSOD1) maturation through interaction with human copper chaperone for SOD1 (hCCS). *Proc. Natl. Acad. Sci. U.S.A., 109*, 13555-60. ↗

Casareno, RL., Waggoner, D., Gitlin, JD. (1998). The copper chaperone CCS directly interacts with copper/zinc superoxide dismutase. *J. Biol. Chem., 273*, 23625-8. ↗

Culotta, VC., Klomp, LW., Strain, J., Casareno, RL., Krems, B., Gitlin, JD. (1997). The copper chaperone for superoxide dismutase. *J. Biol. Chem., 272*, 23469-72. ↗

Rae, TD., Torres, AS., Pufahl, RA., O'Halloran, TV. (2001). Mechanism of Cu,Zn-superoxide dismutase activation by the human metallochaperone hCCS. *J. Biol. Chem., 276*, 5166-76. ↗

Brown, NM., Torres, AS., Doan, PE., O'Halloran, TV. (2004). Oxygen and the copper chaperone CCS regulate posttranslational activation of Cu,Zn superoxide dismutase. *Proc. Natl. Acad. Sci. U.S.A., 101*, 5518-23. ↗

Editions

2013-04-20	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

SOD1:Zn2+ apoenzyme binds CCS:Cu1+ (mitochondrial)

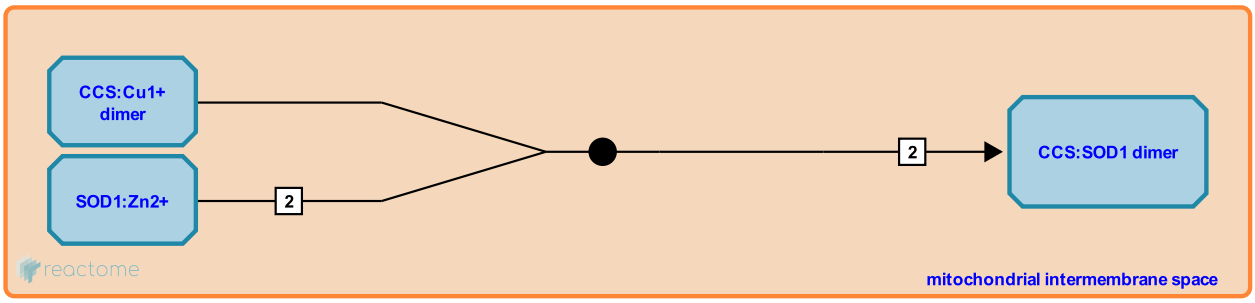
Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3780958

Type: binding

Compartments: mitochondrial intermembrane space

Inferred from: Sod1 apoenzyme binds Ccs (Mus musculus), SOD1:Zn2+ apoenzyme binds CCS:Zn2+:2xCu1+ (Homo sapiens)



As inferred from the cytosolic reaction and from the mouse mitochondrial reaction, Copper chaperone of superoxide dismutase (CCS) transfers a copper(I) atom to a SOD1 monomer that already contains a Zn atom. The reaction proceeds by a two step mechanism in which SOD1 first forms heterodimers with CCS. The amounts of CCS and SOD1 in the intermembrane space appear to be regulated by the concentration of oxygen. Mutations in SOD1 are responsible for familial amyotrophic lateral sclerosis (fALS) and cause unregulated localization and aggregation of SOD1 in the intermembrane space (reviewed in Kawamata and Manfredi 2010).

Followed by: CCS transfers Cu to SOD1 (mitochondrial)

Literature references

Kawamata, H., Manfredi, G. (2010). Import, maturation, and function of SOD1 and its copper chaperone CCS in the mitochondrial intermembrane space. *Antioxid. Redox Signal., 13*, 1375-84.

Editions

2013-06-27	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

CCS transfers Cu to SOD1 (mitochondrial) ↗

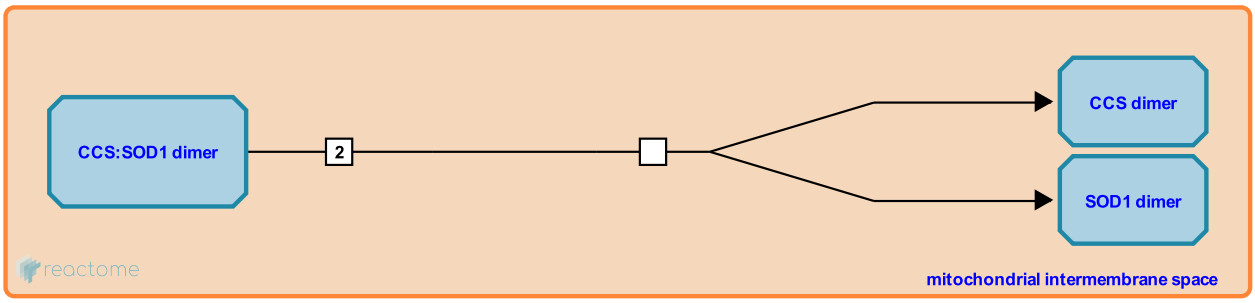
Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3780979

Type: transition

Compartments: mitochondrial intermembrane space

Inferred from: Ccs transfers Cu to Sod1 (Mus musculus), CCS transfers Cu to SOD1 and oxidizes cysteine residues in SOD1 (Homo sapiens)



As inferred from the cytosolic reaction and from the mitochondrial reaction in mouse, Copper chaperone of superoxide dismutase (CCS) transfers a copper(I) atom to a SOD1 monomer that already contains a Zn atom. After initial heterodimerization between SOD1 and CCS, the copper atom is transferred, intramolecular cysteine disulfide bonds are formed in SOD1, and SOD1 dimerizes.

Preceded by: SOD1:Zn2+ apoenzyme binds CCS:Cu1+ (mitochondrial)

Followed by: SOD1 catalyzes 2H+ + O2.- => O2 + H2O2 (mitochondrial intermembrane space)

Editions

2013-06-27	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

ATP7A transfers Cu from ATOX1 to SOD3 ↗

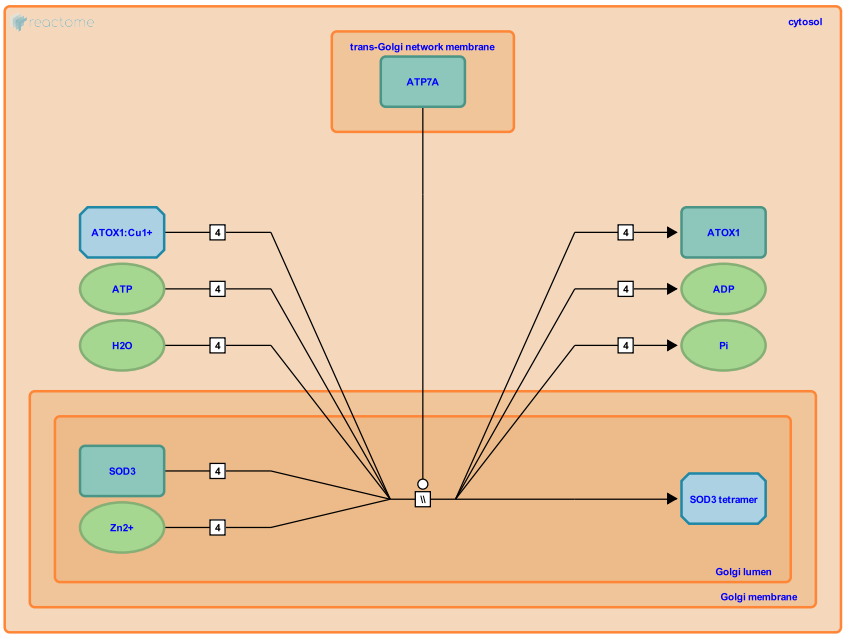
Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3697838

Type: omitted

Compartments: Golgi lumen, cytosol, trans-Golgi network membrane

Inferred from: Atp7a transfers Cu from Atox1 to Sod3 (Mus musculus)



As inferred from mouse, ATP7A (Menke's ATPase, MNK) transports copper from ATOX in the cytosol to SOD3 in the lumen of the trans golgi network. ATP7A and SOD3 directly interact. Mutations in ATP7A cause Menke's disease, a neurodegenerative condition.

Followed by: Secretion of SOD3

Editions

2013-06-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

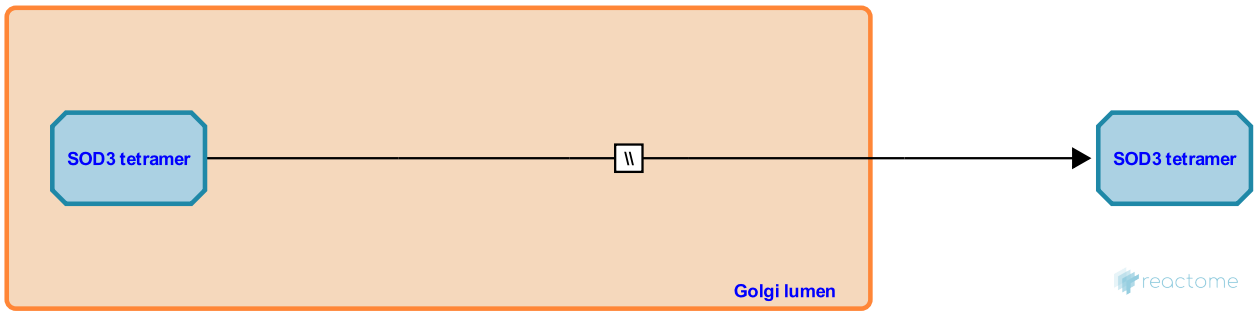
Secretion of SOD3 ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-4837364

Type: omitted

Compartments: Golgi lumen, extracellular region



SOD3 is secreted from cells into the extracellular region. Before secretion a portion of SOD3 molecules are cleaved near the C-terminus at glutamate-227 (glutamate-209 in the mature protein) (Olsen et al. 2004, Karlsson et al. 1993). Removal of the C-terminus prevents interaction with the extracellular matrix so cleaved molecules are soluble. Cleaved and uncleaved molecules are believed to be capable of forming mixed tetramers (Sandstrom et al. 1993).

Preceded by: ATP7A transfers Cu from ATOX1 to SOD3

Followed by: SOD3 catalyzes 2H+ + 2O2.- => O2 + H2O2 (extracellular)

Literature references

Olsen, DA., Petersen, SV., Oury, TD., Valnickova, Z., Thøgersen, IB., Kristensen, T. et al. (2004). The intracellular proteolytic processing of extracellular superoxide dismutase (EC-SOD) is a two-step event. *J. Biol. Chem., 279*, 22152-7. ↗

Sandström, J., Karlsson, K., Edlund, T., Marklund, SL. (1993). Heparin-affinity patterns and composition of extracellular superoxide dismutase in human plasma and tissues. *Biochem. J., 294*, 853-7. ↗

Karlsson, K., Edlund, A., Sandström, J., Marklund, SL. (1993). Proteolytic modification of the heparin-binding affinity of extracellular superoxide dismutase. *Biochem. J., 290*, 623-6. ↗

Editions

2013-11-01	Reviewed	Kavdia, M.
2013-11-01	Authored, Edited	May, B.

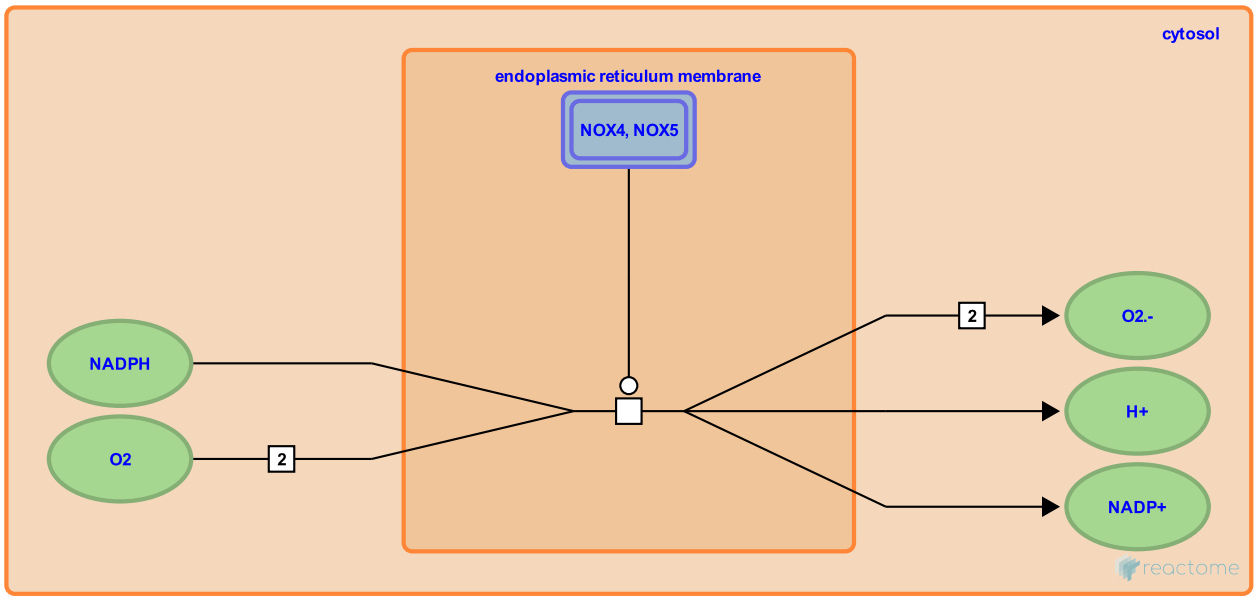
NOX4, NOX5 reduce O2 to O2.-

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-6807557

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



NADPH oxidases 4 and 5 (NOX4, 5) are ER membrane-bound proteins that generates superoxide (O2.-) in endothelial cells (BelAiba et al. 2007). NOX4 functions in association with cytochrome b heterodimer (CYBA:CYBB) on the ER (and nuclear) membrane (Martyn et al. 2006).

Literature references

Martyn, KD., Frederick, LM., von Loehneysen, K., Dinauer, MC., Knaus, UG. (2006). Functional analysis of Nox4 reveals unique characteristics compared to other NADPH oxidases. *Cell. Signal., 18*, 69-82.

BelAiba, RS., Djordjevic, T., Petry, A., Diemer, K., Bonello, S., Banfi, B. et al. (2007). NOX5 variants are functionally active in endothelial cells. *Free Radic. Biol. Med., 42*, 446-59.

Editions

2015-11-03	Authored, Edited	Jassal, B.
2016-01-11	Reviewed	D'Eustachio, P.

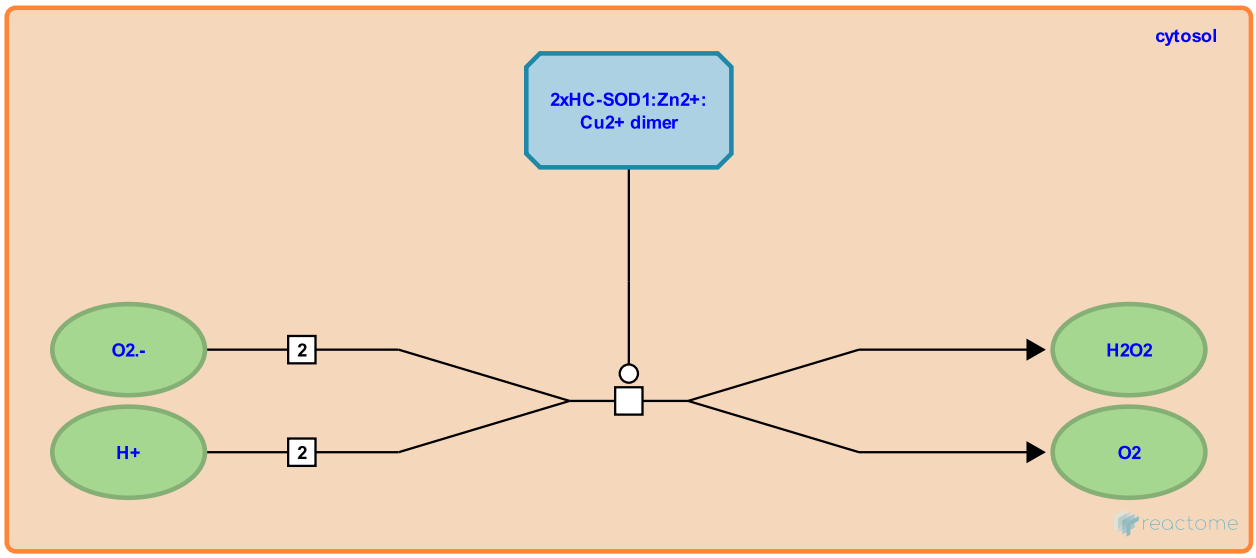
SOD1 catalyzes 2H+ + 2O2.- => O2 + H2O2 (cytosol)

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3299691

Type: transition

Compartments: cytosol



Cu-Zn superoxide dismutase (SOD1), originally known as erythrocuprein, catalyzes the reaction of two molecules of superoxide (O2.-) to yield one molecule of hydrogen peroxide (H2O2) and one molecule of oxygen (O2) (McCord and Fridovich 1969 assayed both bovine and human Cu-Zn superoxide dismutase, the human sample provided by Carrico and Deutsch). Diffusion of hydrogen peroxide, the product of SOD1, across the cytosol is limited (Mishina et al. 2011)

Preceded by: CCS transfers Cu to SOD1 and oxidizes cysteine residues in SOD1

Followed by: PRDX6:GSTP1 catalyzes 2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O, GPX2 catalyzes 2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O, PRDX1,2,5 catalyze TXN reduced + H2O2 => TXN oxidized + 2H2O, 2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O

Literature references

Hartman, JR., Geller, T., Yavin, Z., Bartfeld, D., Kanner, D., Aviv, H. et al. (1986). High-level expression of enzymatically active human Cu/Zn superoxide dismutase in Escherichia coli. *Proc. Natl. Acad. Sci. U.S.A., 83*, 7142-6.

Sugiura, M., Adachi, T., Inoue, H., Ito, Y., Hirano, K. (1981). Purification of superoxide dismutases from human placenta using immunoadsorbent columns. *J. Pharmacobio-dyn., 4*, 245-50.

McCord, JM., Fridovich, I. (1969). Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein). *J. Biol. Chem., 244*, 6049-55.

Mishina, NM., Tyurin-Kuzmin, PA., Markvicheva, KN., Vorotnikov, AV., Tkachuk, VA., Laketa, V. et al. (2011). Does cellular hydrogen peroxide diffuse or act locally?. *Antioxid. Redox Signal., 14*, 1-7.

Editions

2013-04-20	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

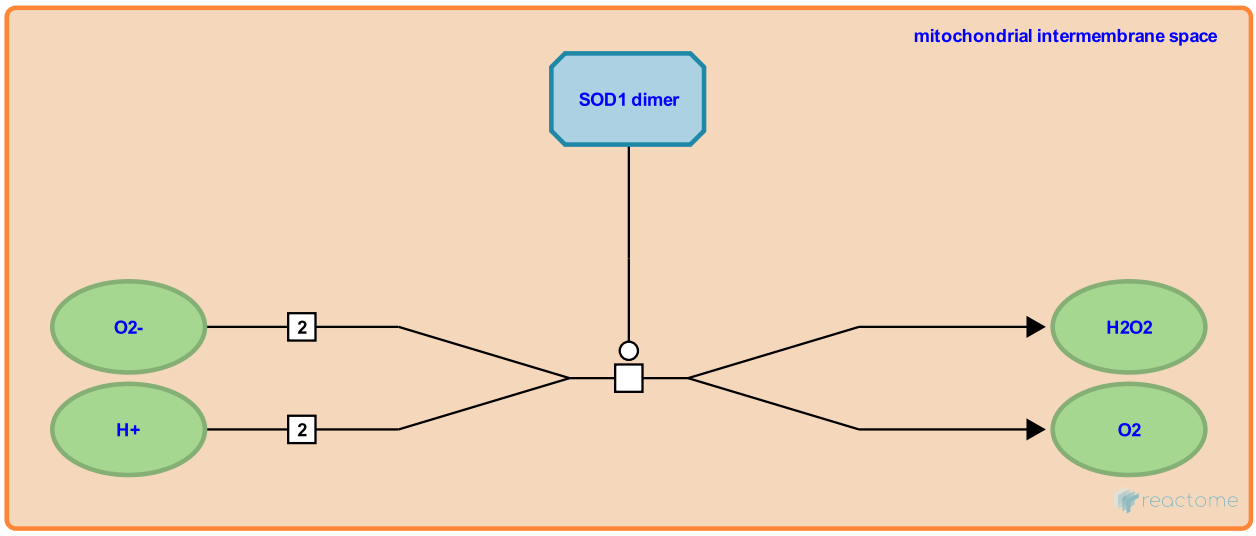
SOD1 catalyzes 2H+ + O2.- => O2 + H2O2 (mitochondrial intermembrane space)

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3777112

Type: transition

Compartments: mitochondrial intermembrane space



A portion of SOD1 is located in the mitochondrial intermembrane space (IMS) where it catalyzes the formation of oxygen (O2) and hydrogen peroxide (H2O2) from superoxide (O2.-) (He et al. 2011, Higgins et al. 2002, inferred from rat in Okado-Matsumoto and Fridovich 2001).

Preceded by: CCS transfers Cu to SOD1 (mitochondrial)

Literature references

He, C., Murthy, S., McCormick, ML., Spitz, DR., Ryan, AJ., Carter, AB. (2011). Mitochondrial Cu,Zn-superoxide dismutase mediates pulmonary fibrosis by augmenting H2O2 generation. *J. Biol. Chem., 286*, 15597-607.

Higgins, CM., Jung, C., Ding, H., Xu, Z. (2002). Mutant Cu, Zn superoxide dismutase that causes motoneuron degeneration is present in mitochondria in the CNS. *J. Neurosci., 22*, RC215.

Okado-Matsumoto, A., Fridovich, I. (2001). Subcellular distribution of superoxide dismutases (SOD) in rat liver: Cu,Zn-SOD in mitochondria. *J. Biol. Chem., 276*, 38388-93.

Editions

2013-06-26	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

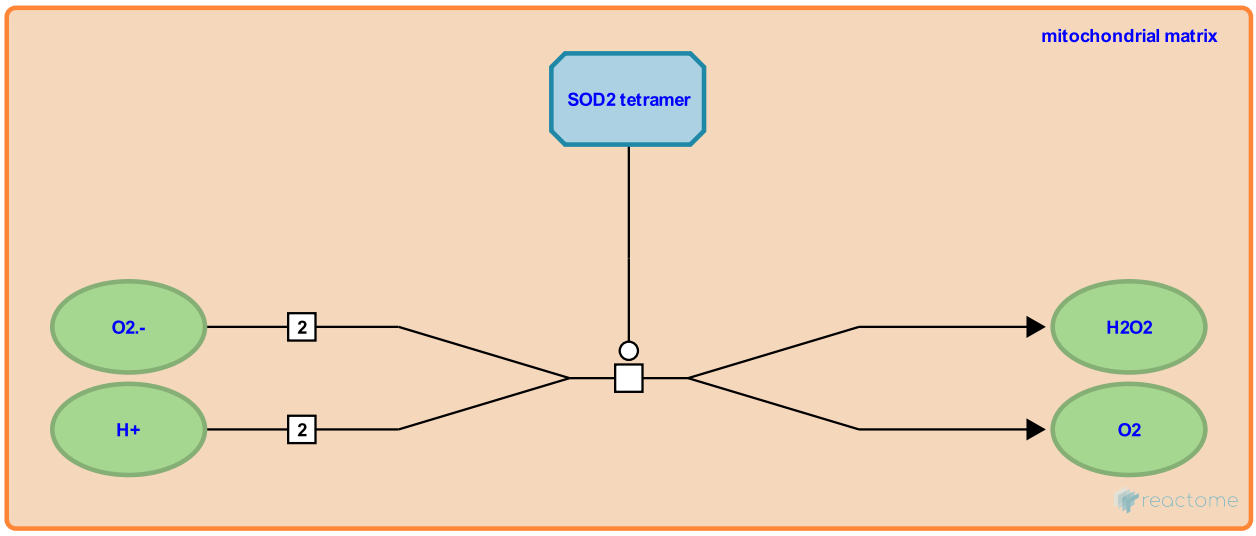
SOD2 catalyzes 2H+ + 2O2.- => O2 + H2O2 (mitochondrial matrix)

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3299680

Type: transition

Compartments: mitochondrial matrix



Mn superoxide dismutase (SOD2) is located in the mitochondrial matrix where it catalyzes the reaction of two molecules of superoxide (O2-.) to form one molecule of oxygen (O2) and one molecule of hydrogen peroxide (H2O2). Data from mouse liver indicate that respiratory complex I leaks superoxide into the matrix and respiratory complex III leaks superoxide into both the matrix and the intermembrane space (Muller et al. 2004). Because of its negative charge superoxide is unable to cross membranes, however hydrogen peroxide, a product of SOD2, is released from mitochondria to the cytosol in proportion to the proton potential (inferred from rat heart mitochondria in Boveris et al. 2006, Korshunov et al. 1997).

Followed by: GPX1 catalyzes 2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O, H2O2 diffuses from the mitochondrial matrix to the cytosol, PRDX3,5 catalyze TXN2 reduced + H2O2 => TXN2 oxidized + 2H2O

Literature references

Hsu, JL., Hsieh, Y., Tu, C., O'Connor, D., Nick, HS., Silverman, DN. (1996). Catalytic properties of human manganese superoxide dismutase. *J. Biol. Chem., 271*, 17687-91.

Silverman, DN., Nick, HS. (2002). Catalytic pathway of manganese superoxide dismutase by direct observation of superoxide. *Meth. Enzymol., 349*, 61-74.

Werber, MM., Greenstein, LA. (1991). Biochemical and stability properties of recombinant human MnSOD. *Free Radic. Res. Commun., 12*, 335-48.

Sugiura, M., Adachi, T., Inoue, H., Ito, Y., Hirano, K. (1981). Purification of superoxide dismutases from human placenta using immunoadsorbent columns. *J. Pharmacobio-dyn., 4*, 245-50.

Matsuda, Y., Suzuki, K., Ookawara, T., Nakata, T., Seo, HG., Kawata, S. et al. (1991). A three-step purification of manganese superoxide dismutase from human liver on both large and small scales. *Protein Expr. Purif., 2*, 170-4.

Editions

2013-04-20	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

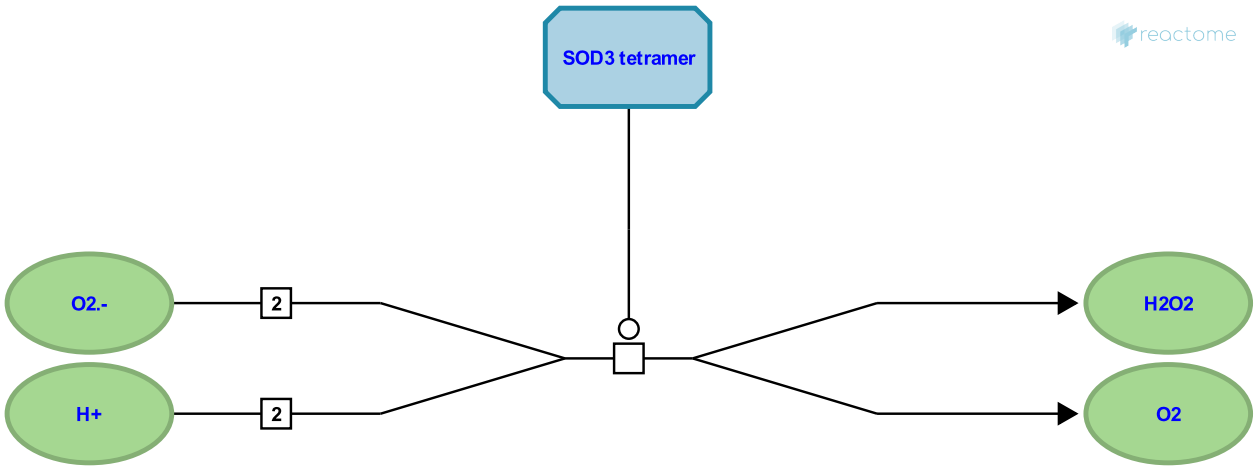
SOD3 catalyzes 2H+ + 2O2.- => O2 + H2O2 (extracellular) ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3299682

Type: transition

Compartments: extracellular region



Extracellular Cu-Zn superoxide dismutase (SOD3) catalyzes the reaction of two molecules of superoxide (O2.-) to form one molecule of oxygen (O2) and one molecule of hydrogen peroxide (H2O2) (Marklund et al. 1982, Marklund 1982)

Preceded by: Secretion of SOD3

Followed by: GPX3 catalyzes 2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O

Literature references

Marklund, SL., Holme, E., Hellner, L. (1982). Superoxide dismutase in extracellular fluids. *Clin. Chim. Acta, 126*, 41-51. ↗

Marklund, SL. (1982). Human copper-containing superoxide dismutase of high molecular weight. *Proc. Natl. Acad. Sci. U.S.A., 79*, 7634-8. ↗

Editions

2013-04-20	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

H2O2 diffuses from the mitochondrial matrix to the cytosol ↗

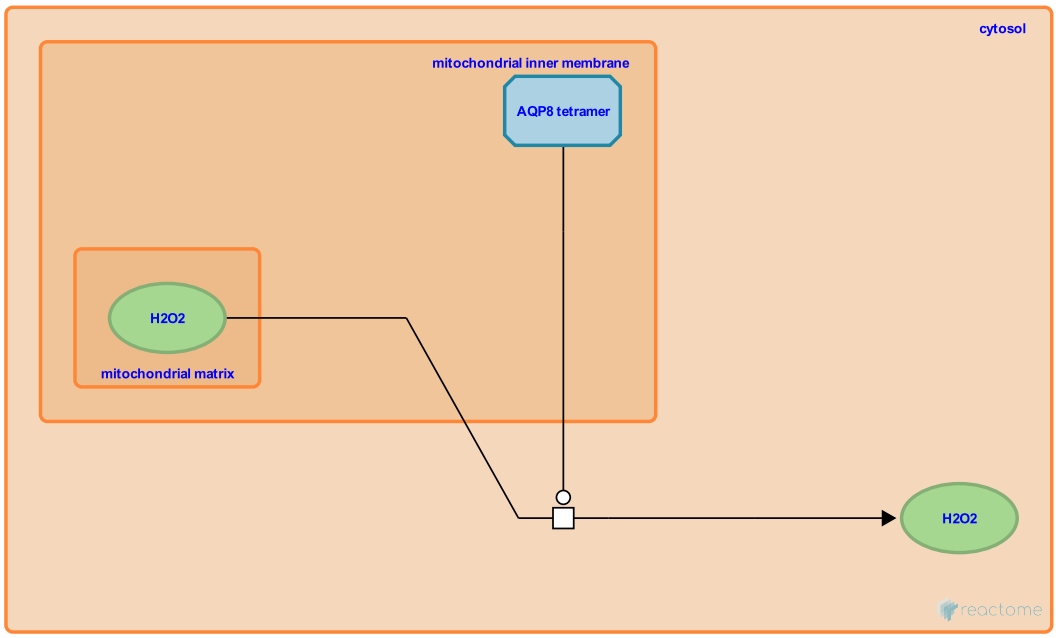
Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3779381

Type: transition

Compartments: cytosol, mitochondrial matrix, mitochondrial inner membrane

Inferred from: H2O2 diffuses from the mitochondrial matrix to the cytosol (Rattus norvegicus)



As inferred from rat heart mitochondria, hydrogen peroxide is released from mitochondria at a rate that is dependent on the membrane potential. Knockdown of Aquaporin-8 (AQP8) in human cells indicates that hydrogen peroxide is able to transit through the water channel of AQP8 located in the inner mitochodrial membrane (Marchissio et al. 2012). The resulting level of cytosolic hydrogen peroxide is hypothesized to signal the state of the mitochondria to regulatory molecules in the cytosol and nucleus (reviewed in Antico Arciuch et al. 2012).

Preceded by: SOD2 catalyzes 2H+ + 2O2.- => O2 + H2O2 (mitochondrial matrix)

Literature references

Marchissio, MJ., Francés, DE., Carnovale, CE., Marinelli, RA. (2012). Mitochondrial aquaporin-8 knockdown in human hepatoma HepG2 cells causes ROS-induced mitochondrial depolarization and loss of viability. *Toxicol. Appl. Pharmacol., 264*, 246-54. ↗

Puente-Maestu, L., Tejedor, A., Lázaro, A., de Miguel, J., Alvarez-Sala, L., González-Aragoneses, F. et al. (2012). Site of mitochondrial reactive oxygen species production in skeletal muscle of chronic obstructive pulmonary disease and its relationship with exercise oxidative stress. *Am. J. Respir. Cell Mol. Biol., 47*, 358-62. ↗

Antico Arciuch, VG., Elguero, ME., Poderoso, JJ., Carreras, MC. (2012). Mitochondrial regulation of cell cycle and proliferation. *Antioxid. Redox Signal., 16*, 1150-80. ↗

Editions

2013-06-26	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

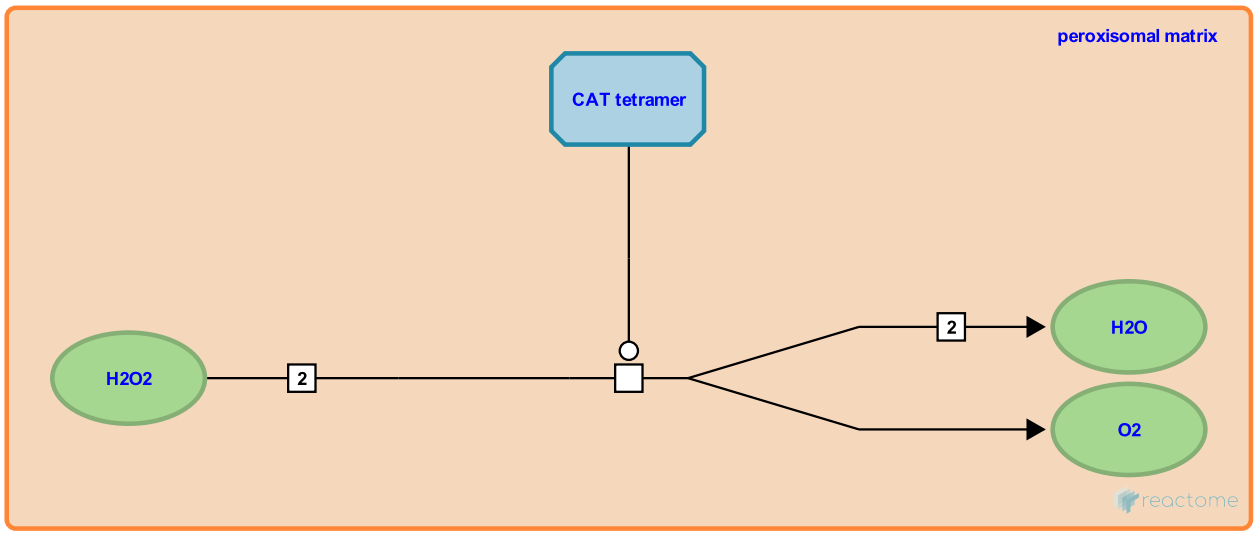
2 H2O2 => O2 + 2 H2O ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-76031

Type: transition

Compartments: peroxisomal matrix



Hydrogen peroxide is generated in the course of peroxisomal fatty acid oxidation and purine catabolism, and is rapidly converted to water and molecular oxygen by the enzyme catalase. This enzyme is widely distributed in the body, but is especially abundant in liver, kidney, and red blood cells.

Literature references

Ogata, M. (1991). Acatalasemia. *Hum Genet, 86*, 331-40. ↗

Putnam, CD., Arvai, AS., Bourne, Y., Tainer, JA. (2000). Active and inhibited human catalase structures: ligand and NADPH binding and catalytic mechanism. *J Mol Biol, 296*, 295-309. ↗

Editions

2003-09-15	Authored	D'Eustachio, P.
2019-08-16	Edited	D'Eustachio, P.

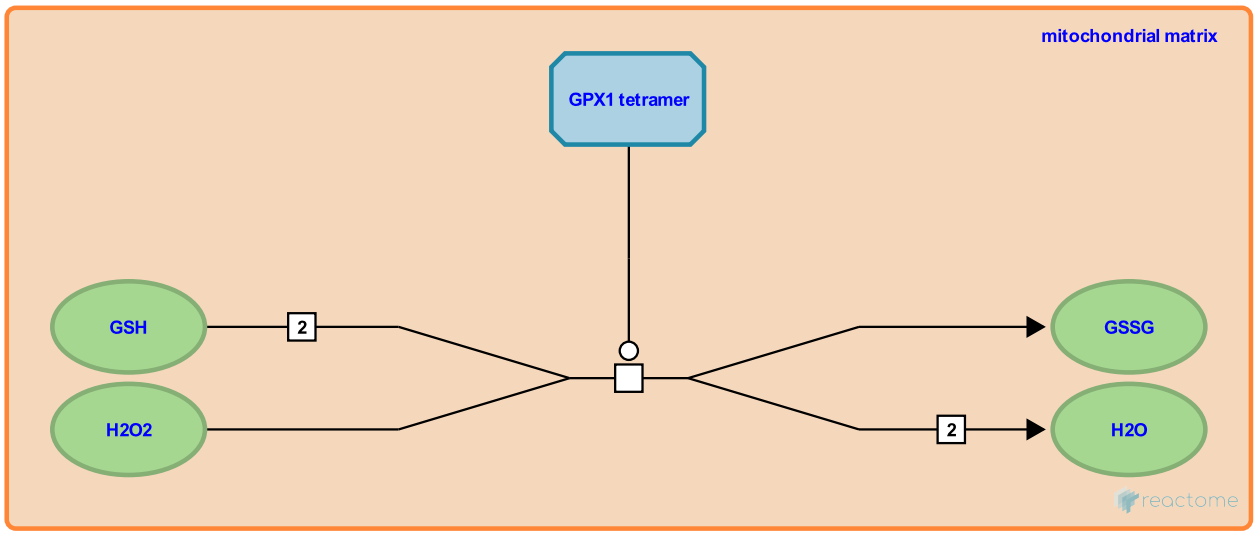
GPX1 catalyzes 2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3323013

Type: transition

Compartments: mitochondrial matrix



Glutathione peroxidase 1 (GPX1) located in the mitochondrial matrix uses glutathione to reduce hydrogen peroxide (H2O2) to yield oxidized glutathione and water (Legault et al. 2000, Li et al. 2000, Faucher et al. 2003). As inferred from rat mitochondria, GPX1 is the major determinant of steady-state hydrogen peroxide levels (Antunes et al. 2002).

Preceded by: SOD2 catalyzes 2H+ + 2O2.- => O2 + H2O2 (mitochondrial matrix)

Followed by: GSR catalyzes glutathione (oxidized) + NADPH + H+ => 2 glutathione (reduced) + NADP+

Literature references

Legault, J., Carrier, C., Petrov, P., Renard, P., Remacle, J., Mirault, ME. (2000). Mitochondrial GPx1 decreases induced but not basal oxidative damage to mtDNA in T47D cells. *Biochem. Biophys. Res. Commun., 272*, 416-22. ↗

Li, S., Yan, T., Yang, JQ., Oberley, TD., Oberley, LW. (2000). The role of cellular glutathione peroxidase redox regulation in the suppression of tumor cell growth by manganese superoxide dismutase. *Cancer Res., 60*, 3927-39. ↗

Faucher, K., Rabinovitch-Chable, H., Barrière, G., Cook-Moreau, J., Rigaud, M. (2003). Overexpression of cytosolic glutathione peroxidase (GPX1) delays endothelial cell growth and increases resistance to toxic challenges. *Biochimie, 85*, 611-7. ↗

Antunes, F., Han, D., Cadenas, E. (2002). Relative contributions of heart mitochondria glutathione peroxidase and catalase to H(2)O(2) detoxification in in vivo conditions. *Free Radic. Biol. Med., 33*, 1260-7. ↗

Editions

2013-05-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

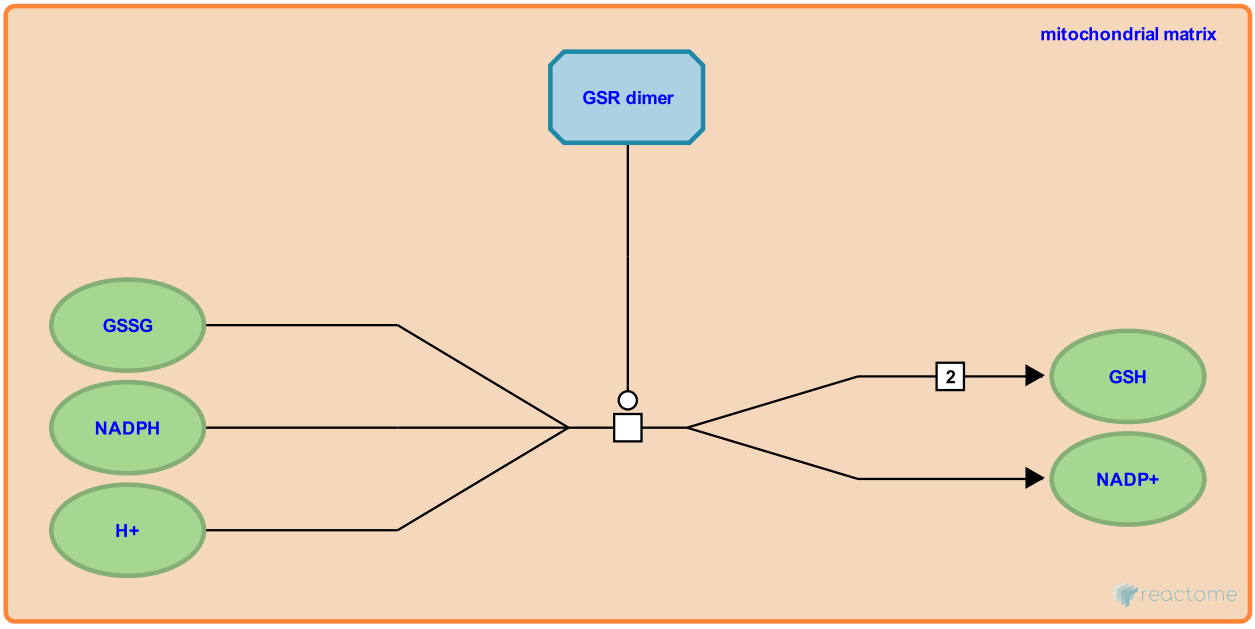
GSR catalyzes glutathione (oxidized) + NADPH + H+ => 2 glutathione (reduced) + NADP+ ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3323079

Type: transition

Compartments: mitochondrial matrix



Glutathione reductase (GSR) in the mitochondrial matrix regenerates reduced glutathione from oxidized glutathione and NADPH (Berkholz et al. 2008).

Preceded by: GPX1 catalyzes 2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O

Literature references

Berkholz, DS., Faber, HR., Savvides, SN., Karplus, PA. (2008). Catalytic cycle of human glutathione reductase near 1 A resolution. *J. Mol. Biol., 382*, 371-84. ↗

Editions

2013-05-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

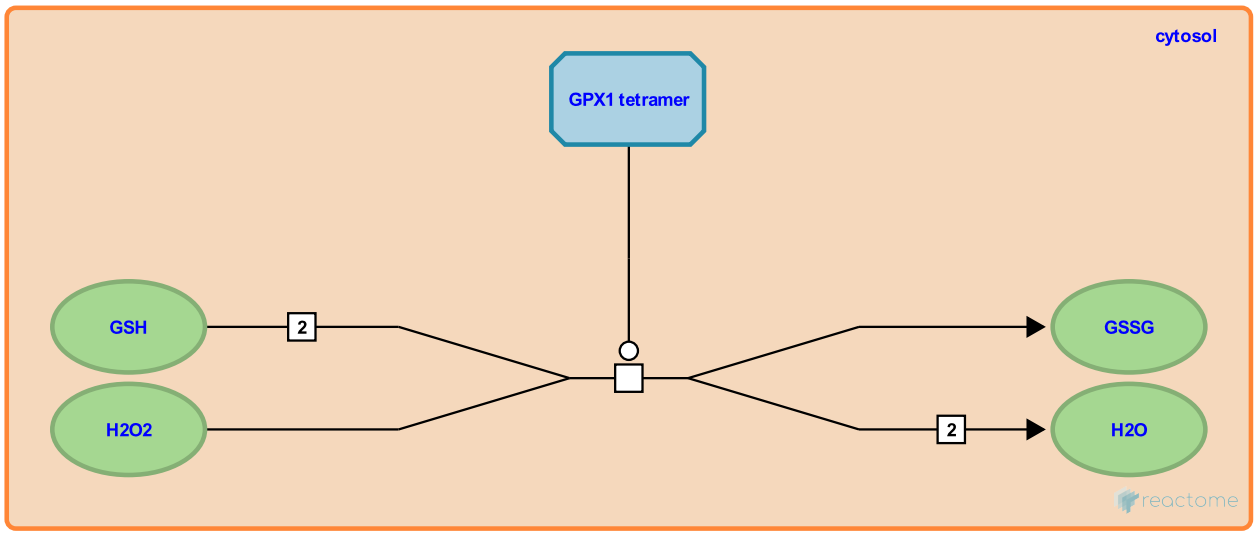
2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-71676

Type: transition

Compartments: cytosol



Cytosolic glutathione peroxidase (GPX1) tetramer catalyzes the reaction of reduced glutathione and hydrogen peroxide to form reduced glutathione and water (Chu et al. 1993).

Preceded by: glutathione (oxidized) + NADPH + H+ => 2 glutathione (reduced) + NADP+, SOD1 catalyzes 2H+ + 2O2.- => O2 + H2O2 (cytosol)

Literature references

Chu, FF., Doroshow, JH., Esworthy, RS. (1993). Expression, characterization, and tissue distribution of a new cellular selenium-dependent glutathione peroxidase, GSHPx-GI. *J Biol Chem, 268*, 2571-6. ↗

Awasthi, YC., Beutler, E., Srivastava, SK. (1975). Purification and properties of human erythrocyte glutathione peroxidase. *J. Biol. Chem., 250*, 5144-9. ↗

Cho, CS., Lee, S., Lee, GT., Woo, HA., Choi, EJ., Rhee, SG. (2010). Irreversible inactivation of glutathione peroxidase 1 and reversible inactivation of peroxiredoxin II by H2O2 in red blood cells. *Antioxid. Redox Signal., 12*, 1235-46. ↗

Takahashi, K., Newburger, PE., Cohen, HJ. (1986). Glutathione peroxidase protein. Absence in selenium deficiency states and correlation with enzymatic activity. *J. Clin. Invest., 77*, 1402-4. ↗

Editions

2005-04-29	Authored, Edited	Vastrik, I.
2006-03-15	Edited	D'Eustachio, P.

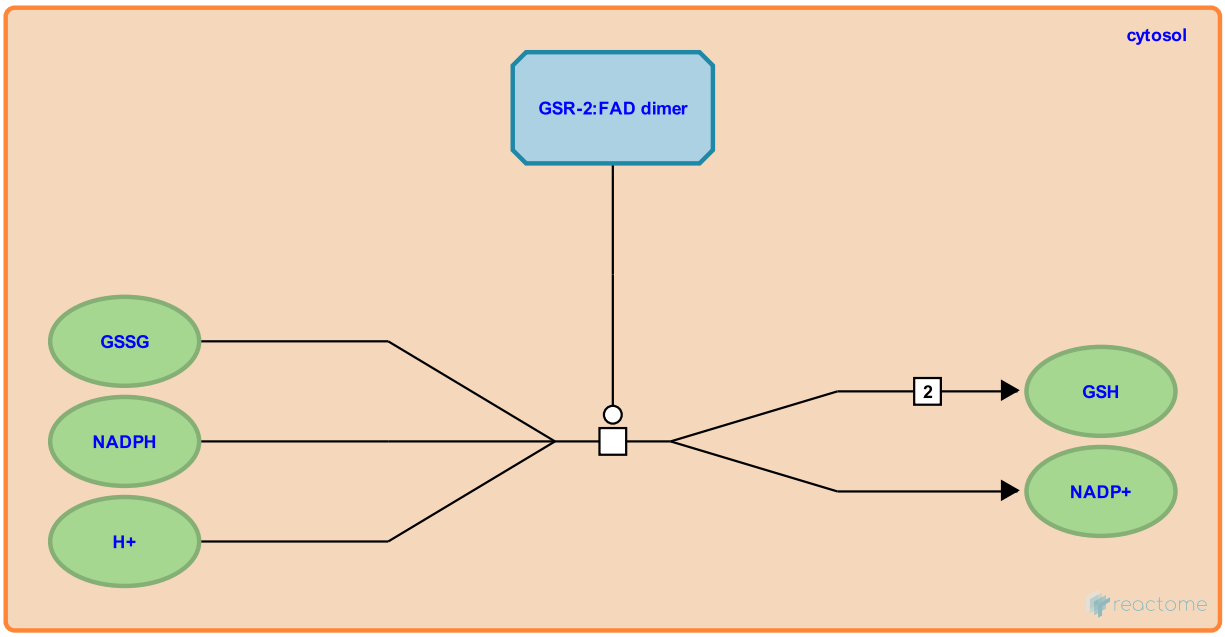
glutathione (oxidized) + NADPH + H+ => 2 glutathione (reduced) + NADP+ ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-71682

Type: transition

Compartments: cytosol



Cytosolic glutathione reductase catalyzes the reaction of glutathione (oxidized) and NADPH + H+ to form two molecules of glutathione (reduced) and NADP+ (Scott et al. 1963, Loos et al. 1976). Deficiency of glutathione reductase can cause hemolytic anemia.

Followed by: 2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O

Literature references

Loos, H., Roos, D., Weening, R., Houwerzijl, J. (1976). Familial deficiency of glutathione reductase in human blood cells. *Blood, 48*, 53-62. ↗

SCOTT, EM., DUNCAN, IW., EKSTRAND, V. (1963). PURIFICATION AND PROPERTIES OF GLUTATHIONE REDUCTASE OF HUMAN ERYTHROCYTES. *J. Biol. Chem., 238*, 3928-33. ↗

Editions

2004-03-17	Authored, Edited	D'Eustachio, P.
2005-04-29	Edited	Vastrik, I.
2010-02-05	Revised	D'Eustachio, P.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

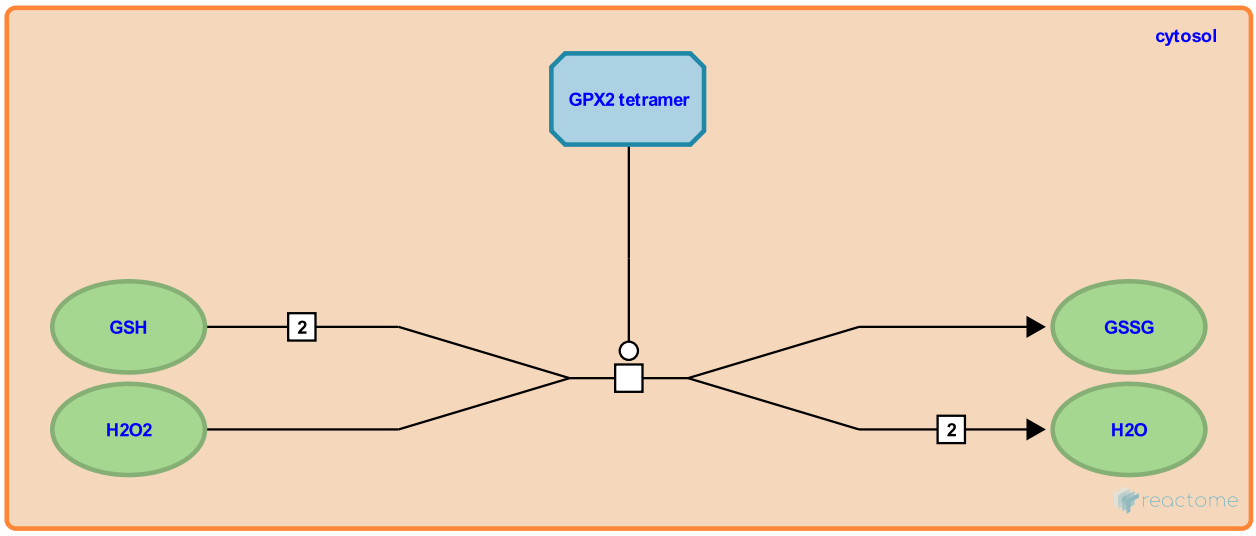
GPX2 catalyzes 2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3341277

Type: transition

Compartments: cytosol



GPX2 (located in the gastrointestinal tract, also called GSHPx-GI, GPX-GI, and GI-GPx), like glutathione peroxidase 1 (GPX1, ubiquitous), reduces one molecule of hydrogen peroxide (H2O2) with two molecules of glutathione to yield one molecule of oxidized glutathione (glutathione disulfide, GSSG) and two molecules of water (Chu et al. 1998).

Preceded by: SOD1 catalyzes 2H+ + 2O2.- => O2 + H2O2 (cytosol)

Literature references

Chu, FF., Doroshow, JH., Esworthy, RS. (1993). Expression, characterization, and tissue distribution of a new cellular selenium-dependent glutathione peroxidase, GSHPx-GI. *J Biol Chem, 268*, 2571-6. ↗

Editions

2013-05-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

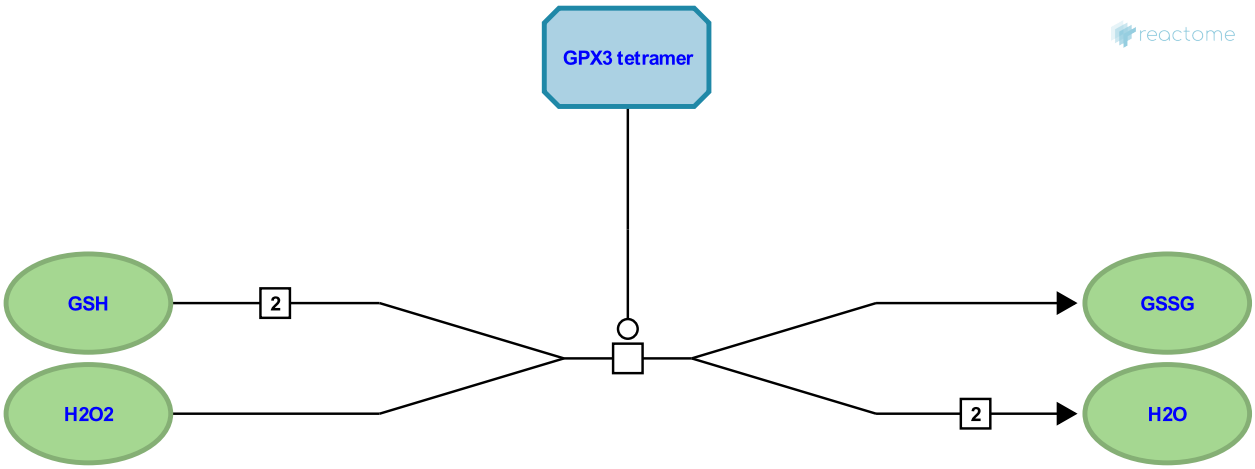
GPX3 catalyzes 2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3341397

Type: transition

Compartments: extracellular region



Glutathione peroxidase 3 (GPX3) in plasma reduces hydrogen peroxide (H2O2) with glutathione to yield oxidized glutathione and water (Maddipati and Marnett 1987, Takahashi et al. 1987, Chung et al. 2009, Ottaviano et al. 2009). Glutathione is synthesized in the liver and exported into the plasma.

Preceded by: SOD3 catalyzes 2H+ + 2O2.- => O2 + H2O2 (extracellular)

Literature references

Ottaviano, FG., Tang, SS., Handy, DE., Loscalzo, J. (2009). Regulation of the extracellular antioxidant selenoprotein plasma glutathione peroxidase (GPx-3) in mammalian cells. *Mol. Cell. Biochem., 327*, 111-26. ↗

Chung, SS., Kim, M., Youn, BS., Lee, NS., Park, JW., Lee, IK. et al. (2009). Glutathione peroxidase 3 mediates the antioxidant effect of peroxisome proliferator-activated receptor gamma in human skeletal muscle cells. *Mol. Cell. Biol., 29*, 20-30. ↗

Maddipati, KR., Marnett, LJ. (1987). Characterization of the major hydroperoxide-reducing activity of human plasma. Purification and properties of a selenium-dependent glutathione peroxidase. *J. Biol. Chem., 262*, 17398-403. ↗

Takahashi, K., Avissar, N., Whitin, J., Cohen, H. (1987). Purification and characterization of human plasma glutathione peroxidase: a selenoglycoprotein distinct from the known cellular enzyme. *Arch. Biochem. Biophys., 256*, 677-86. ↗

Editions

2013-05-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

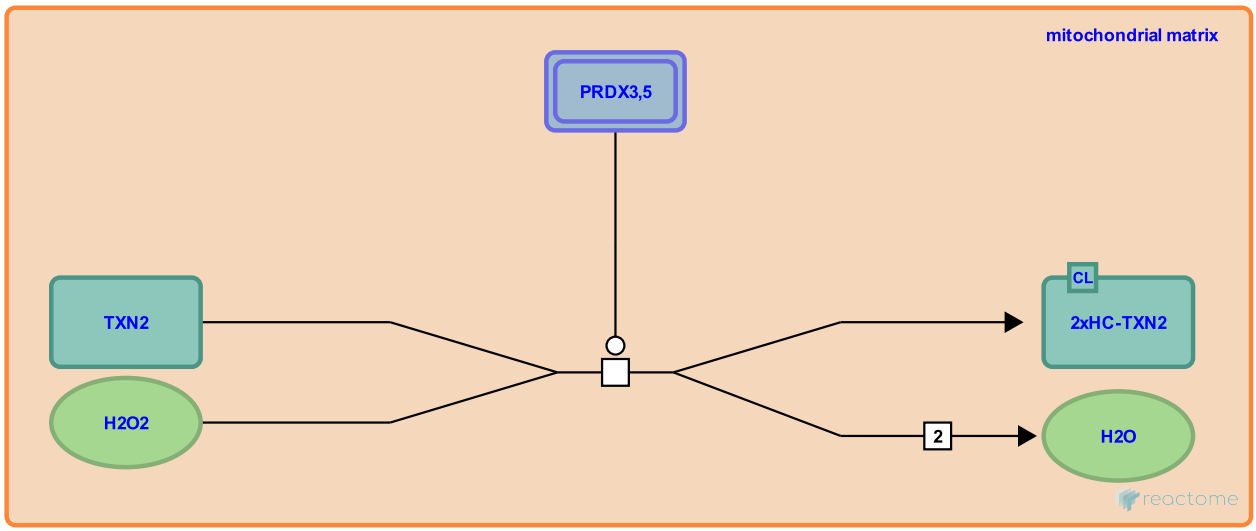
PRDX3,5 catalyze TXN2 reduced + H2O2 => TXN2 oxidized + 2H2O ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3322995

Type: transition

Compartments: mitochondrial matrix



Peroxiredoxin 3 (PRDX3) and PRDX5 in the mitochondrial matrix reduce hydrogen peroxide (H2O2) with thioredoxin to yield oxidized thioredoxin and water (Yamashita et al. 1999, Knoops et al. 1999, Cao et al. 2007, Nagy et al. 2011). Reduced PRDX5 is a monomer (Declercq et al. 2001) and oxidized PRDX5 is a dimer (Evrard et al. 2004) therefore the enzyme may cycle between states.

Preceded by: SOD2 catalyzes 2H+ + 2O2.- => O2 + H2O2 (mitochondrial matrix), TXNRD2 catalyzes the reduction of TXN2 by NADPH

Followed by: TXNRD2 catalyzes the reduction of TXN2 by NADPH

Literature references

Nagy, P., Karton, A., Betz, A., Peskin, AV., Pace, P., O'Reilly, RJ. et al. (2011). Model for the exceptional reactivity of peroxiredoxins 2 and 3 with hydrogen peroxide: a kinetic and computational study. *J. Biol. Chem., 286*, 18048-55. ↗

Cao, Z., Bhella, D., Lindsay, JG. (2007). Reconstitution of the mitochondrial PrxIII antioxidant defence pathway: general properties and factors affecting PrxIII activity and oligomeric state. *J. Mol. Biol., 372*, 1022-33. ↗

Knoops, B., Clippe, A., Bogard, C., Arsalane, K., Wattiez, R., Hermans, C. et al. (1999). Cloning and characterization of AOEB166, a novel mammalian antioxidant enzyme of the peroxiredoxin family. *J. Biol. Chem., 274*, 30451-8. ↗

Yamashita, H., Avraham, S., Jiang, S., London, R., Van Veldhoven, PP., Subramani, S. et al. (1999). Characterization of human and murine PMP20 peroxisomal proteins that exhibit antioxidant activity in vitro. *J. Biol. Chem., 274*, 29897-904. ↗

Declercq, JP., Evrard, C., Clippe, A., Stricht, DV., Bernard, A., Knoops, B. (2001). Crystal structure of human peroxiredoxin 5, a novel type of mammalian peroxiredoxin at 1.5 A resolution. *J. Mol. Biol., 311*, 751-9. ↗

Editions

2013-05-05	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

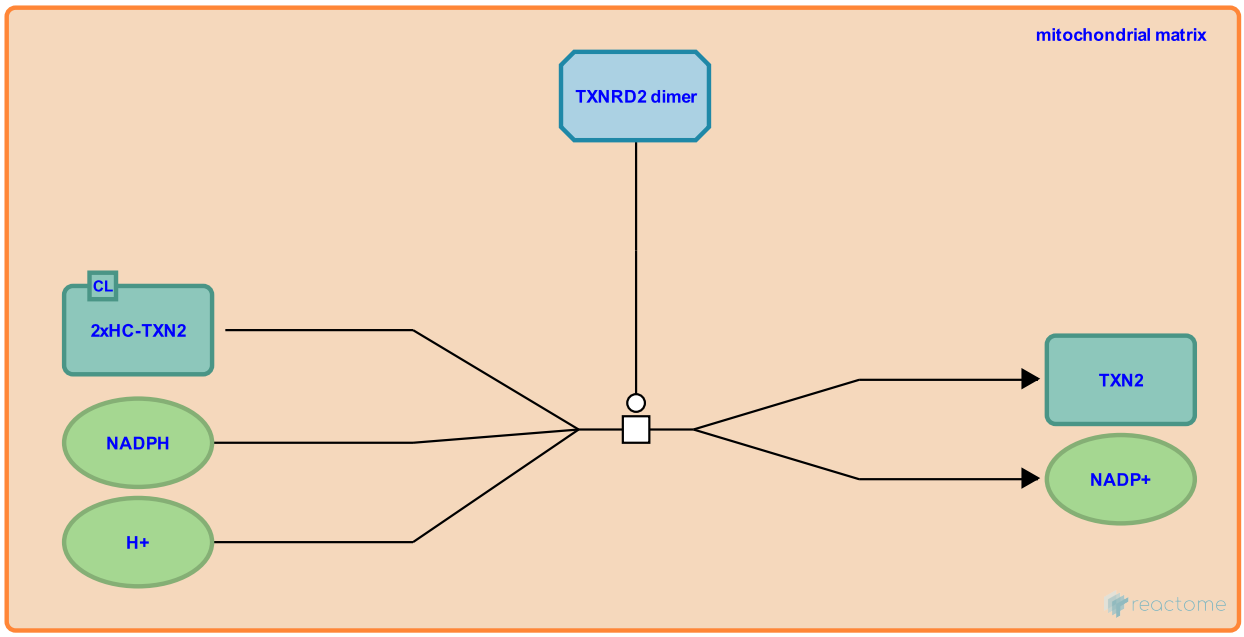
TXNRD2 catalyzes the reduction of TXN2 by NADPH ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3323050

Type: transition

Compartments: mitochondrial matrix



Thioredoxin reductase 2 (TXNRD2) in the mitochondrial matrix regenerates reduced thioredoxin (TXN) by reacting oxidized thioredoxin with NADPH (Gasdaska et al. 1999, Cao et al. 2007).

Preceded by: PRDX3,5 catalyze TXN2 reduced + H2O2 => TXN2 oxidized + 2H2O

Followed by: PRDX5 reduces peroxynitrite to nitrite using TXN2, PRDX3,5 catalyze TXN2 reduced + H2O2 => TXN2 oxidized + 2H2O

Literature references

Cao, Z., Bhella, D., Lindsay, JG. (2007). Reconstitution of the mitochondrial PrxIII antioxidant defence pathway: general properties and factors affecting PrxIII activity and oligomeric state. *J. Mol. Biol., 372*, 1022-33. ↗

Gasdaska, PY., Berggren, MM., Berry, MJ., Powis, G. (1999). Cloning, sequencing and functional expression of a novel human thioredoxin reductase. *FEBS Lett., 442*, 105-11. ↗

Editions

2013-05-05	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

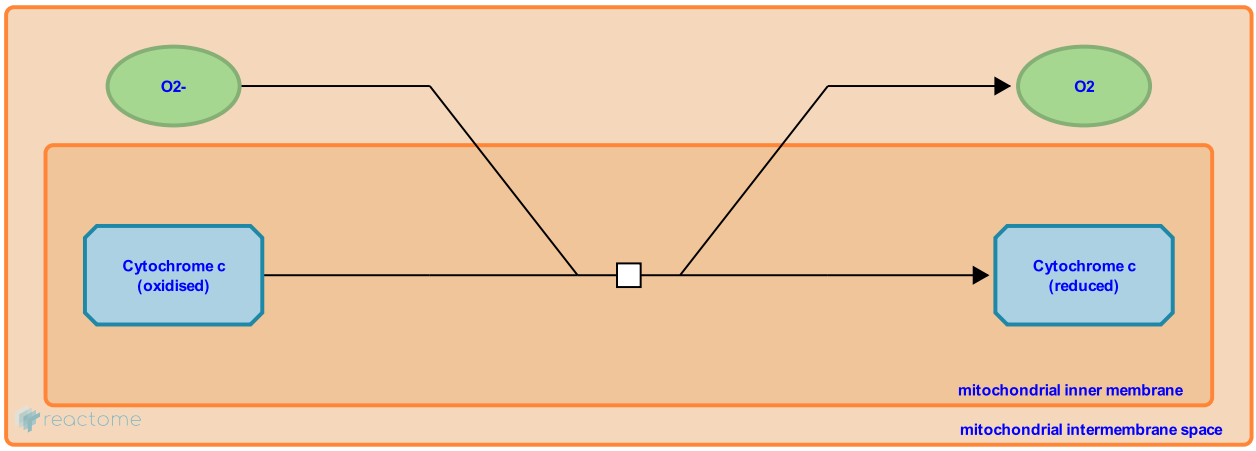
Superoxide reduces cytochrome c ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3341294

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial intermembrane space



Superoxide can reduce cytochrome c in the intermembrane space (Wegerich et al. 2013, and inferred from other mammals in Butler et al. 1975, Koppenol et al. 1976, Butler et al. 1982). Superoxide has been shown in rat and mouse mitochondria to be released into the intermembrane space by the complex III of the respiratory chain (Han et al. 2001, Muller et al. 2004).

Literature references

Wegerich, F., Giachetti, A., Allegrozzi, M., Lisdat, F., Turano, P. (2013). Mechanistic insights into the superoxide-cytochrome c reaction by lysine surface scanning. *J. Biol. Inorg. Chem., 18*, 429-40. ↗

Butler, J., Koppenol, WH., Margoliash, E. (1982). Kinetics and mechanism of the reduction of ferricytochrome c by the superoxide anion. *J. Biol. Chem., 257*, 10747-50. ↗

Koppenol, WH., van Buuren, KJ., Butler, J., Braams, R. (1976). The kinetics of the reduction of cytochrome c by the superoxide anion radical. *Biochim. Biophys. Acta, 449*, 157-68. ↗

Butler, J., Jayson, GG., Swallow, AJ. (1975). The reaction between the superoxide anion radical and cytochrome c. *Biochim. Biophys. Acta, 408*, 215-22. ↗

Han, D., Williams, E., Cadenas, E. (2001). Mitochondrial respiratory chain-dependent generation of superoxide anion and its release into the intermembrane space. *Biochem. J., 353*, 411-6. ↗

Editions

2013-05-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

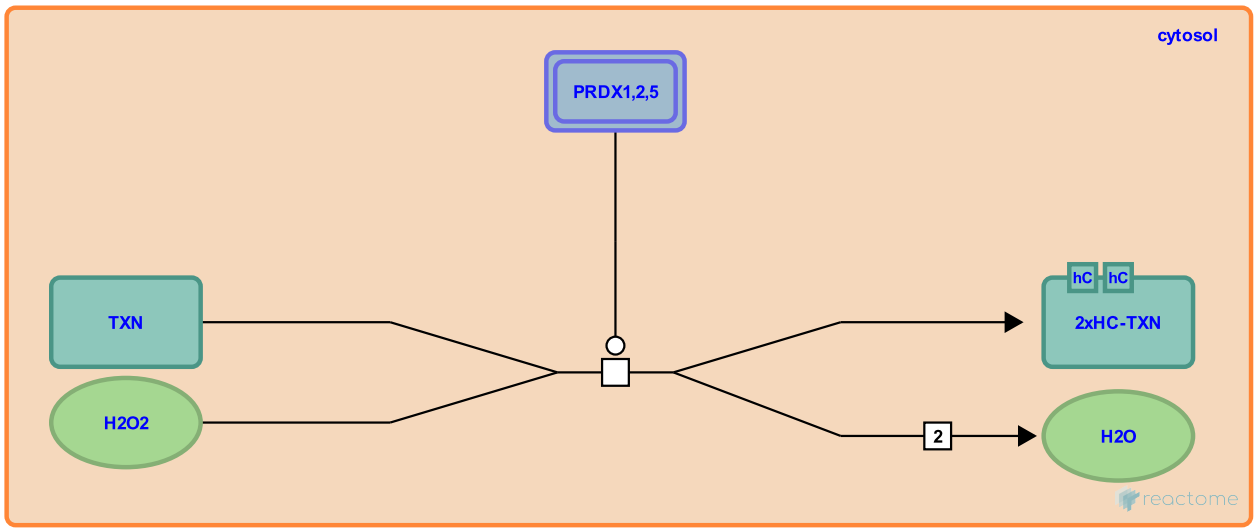
PRDX1,2,5 catalyze TXN reduced + H2O2 => TXN oxidized + 2H2O ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3341343

Type: transition

Compartments: cytosol



Peroxiredoxin 1 (PRDX1), PRDX2, and PRDX5 in the cytosol reduce hydrogen peroxide (H2O2) with thioredoxin yielding oxidized thioredoxin and water (Yamashita et al. 1999, Lee et al. 2007, Nagy et al. 2011).

Preceded by: SOD1 catalyzes 2H+ + 2O2.- => O2 + H2O2 (cytosol), thioredoxin, oxidized + NADPH + H+ => thioredoxin, reduced + NADP+

Literature references

Nagy, P., Karton, A., Betz, A., Peskin, AV., Pace, P., O'Reilly, RJ. et al. (2011). Model for the exceptional reactivity of peroxiredoxins 2 and 3 with hydrogen peroxide: a kinetic and computational study. *J. Biol. Chem., 286*, 18048-55. ↗

Lee, W., Choi, KS., Riddell, J., Ip, C., Ghosh, D., Park, JH. et al. (2007). Human peroxiredoxin 1 and 2 are not duplicate proteins: the unique presence of CYS83 in Prx1 underscores the structural and functional differences between Prx1 and Prx2. *J. Biol. Chem., 282*, 22011-22. ↗

Yamashita, H., Avraham, S., Jiang, S., London, R., Van Veldhoven, PP., Subramani, S. et al. (1999). Characterization of human and murine PMP20 peroxisomal proteins that exhibit antioxidant activity in vitro. *J. Biol. Chem., 274*, 29897-904. ↗

Editions

2013-05-05	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

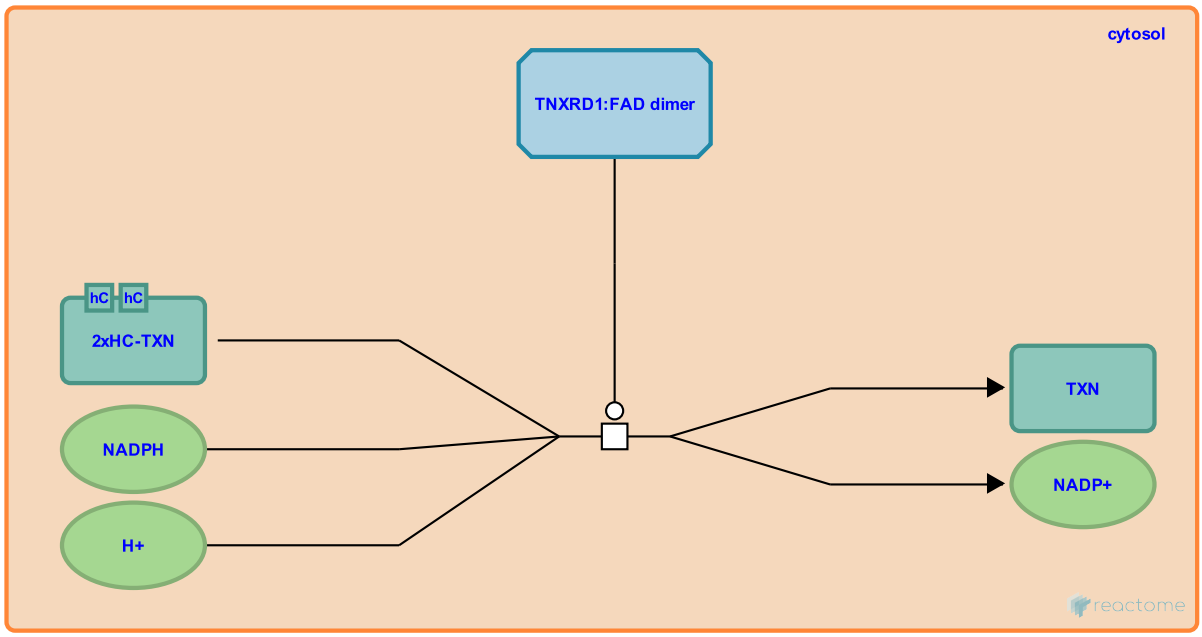
thioredoxin, oxidized + NADPH + H+ => thioredoxin, reduced + NADP+ ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-73646

Type: transition

Compartments: cytosol



Cytosolic thioredoxin reductase catalyzes the reaction of thioredoxin, oxidized and NADPH + H+ to form thioredoxin, reduced and NADP+ (Urig et al. 2006).

Followed by: PRDX5 reduces peroxynitrite to nitrite using TXN, PRDX1,2,5 catalyze TXN reduced + H2O2 => TXN oxidized + 2H2O

Literature references

Urig, S., Lieske, J., Fritz-Wolf, K., Irmler, A., Becker, K. (2006). Truncated mutants of human thioredoxin reductase 1 do not exhibit glutathione reductase activity. *FEBS Lett, 580*, 3595-600. ↗

Editions

2003-06-17	Authored, Edited	Jassal, B.
2010-02-05	Edited, Revised	D'Eustachio, P.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

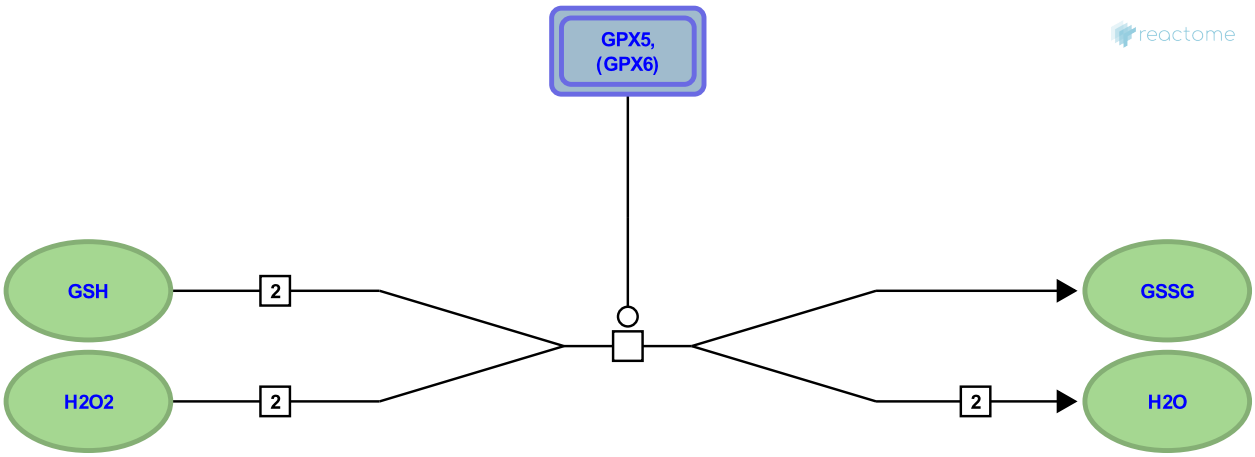
GPX5,6 reduce H2O2 to H2O ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-6799695

Type: transition

Compartments: extracellular region



Epididymal secretory glutathione peroxidase (GPX5), a secreted and selenium-independent isoform of glutathione peroxidases, is present in very low levels in human sperm ejaculate. GPX5 has the potential to reduce hydrogen peroxide (H2O2) using glutathione (GSH), based on activity observed in rat and pig forms of the enzyme but its role in human epidydimis is unknown (Hall et al. 1998). Glutathione peroxidase 6 (GPX6) is thought to have peroxidase activity based on sequence similarity to GPX5.

Literature references

Hall, L., Williams, K., Perry, AC., Frayne, J., Jury, JA. (1998). The majority of human glutathione peroxidase type 5 (GPX5) transcripts are incorrectly spliced: implications for the role of GPX5 in the male reproductive tract. *Biochem. J., 333*, 5-9. ↗

Editions

2015-09-25	Authored, Edited	Jassal, B.
2016-01-11	Reviewed	D'Eustachio, P.

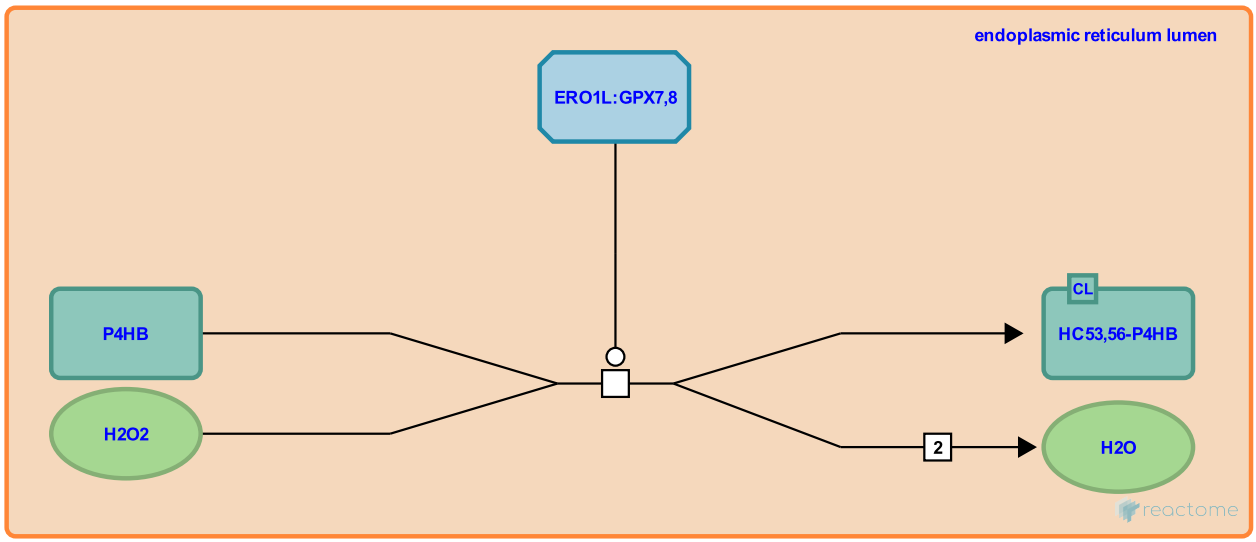
GPX7,8 catalyze peroxidation of P4HB (PDI) ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3341296

Type: transition

Compartments: endoplasmic reticulum lumen



Glutathione peroxidase 7 (GPX7) and GPX8 are atypical glutathione peroxidases that catalyze the peroxidation of protein disulfide isomerases, such as PDI (P4HB) (Nguyen et al. 2011 and inferred from mouse in Bosello-Travain et al. 2013). GPX7 and GPX8 are each able to form heterodimers with the sulfhydryl oxidase ERO1alpha (ERO1L) in the endoplasmic reticulum lumen. It is hypothesized that GPX7 and GPX8 use hydrogen peroxide produced by ERO1L.

Literature references

Nguyen, VD., Saaranen, MJ., Karala, AR., Lappi, AK., Wang, L., Raykhel, IB. et al. (2011). Two endoplasmic reticulum PDI peroxidases increase the efficiency of the use of peroxide during disulfide bond formation. *J. Mol. Biol. , 406*, 503-15. ↗

Bosello-Travain, V., Conrad, M., Cozza, G., Negro, A., Quartesan, S., Rossetto, M. et al. (2013). Protein disulfide isomerase and glutathione are alternative substrates in the one Cys catalytic cycle of glutathione peroxidase 7. *Biochim. Biophys. Acta, 1830*, 3846-57. ↗

Editions

2013-05-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

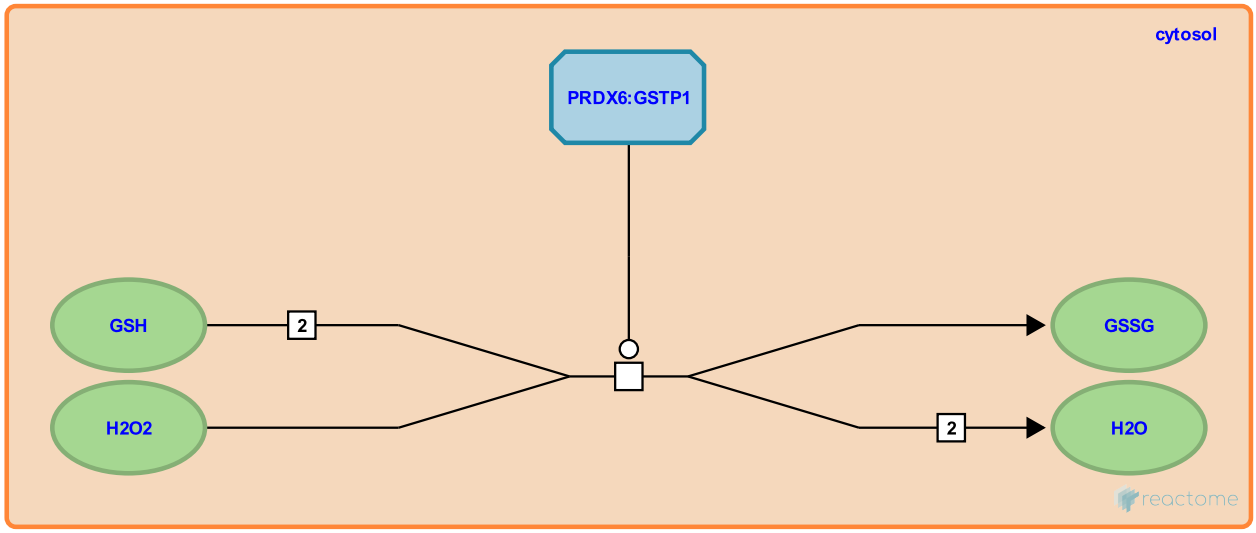
PRDX6:GSTP1 catalyzes 2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3343700

Type: transition

Compartments: cytosol



Peroxiredoxin 6 (PRDX6) forms a heterodimer with GSTP1 (Pi Glutathione transferase) and catalyzes the reduction of hydrogen peroxide (H2O2) by glutathione to yield oxidized glutathione and water (Ralat et al. 2006, Ralat et al. 2008, Zhou et al. 2013).

Preceded by: SOD1 catalyzes 2H+ + 2O2.- => O2 + H2O2 (cytosol)

Literature references

Ralat, LA., Misquitta, SA., Manevich, Y., Fisher, AB., Colman, RF. (2008). Characterization of the complex of glutathione S-transferase pi and 1-cysteine peroxiredoxin. *Arch. Biochem. Biophys., 474*, 109-18. ↗

Ralat, LA., Manevich, Y., Fisher, AB., Colman, RF. (2006). Direct evidence for the formation of a complex between 1-cysteine peroxiredoxin and glutathione S-transferase pi with activity changes in both enzymes. *Biochemistry, 45*, 360-72. ↗

Zhou, S., Lien, YC., Shuvaeva, T., DeBolt, K., Feinstein, SI., Fisher, AB. (2013). Functional interaction of glutathione S-transferase pi and peroxiredoxin 6 in intact cells. *Int. J. Biochem. Cell Biol., 45*, 401-7. ↗

Editions

2013-05-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

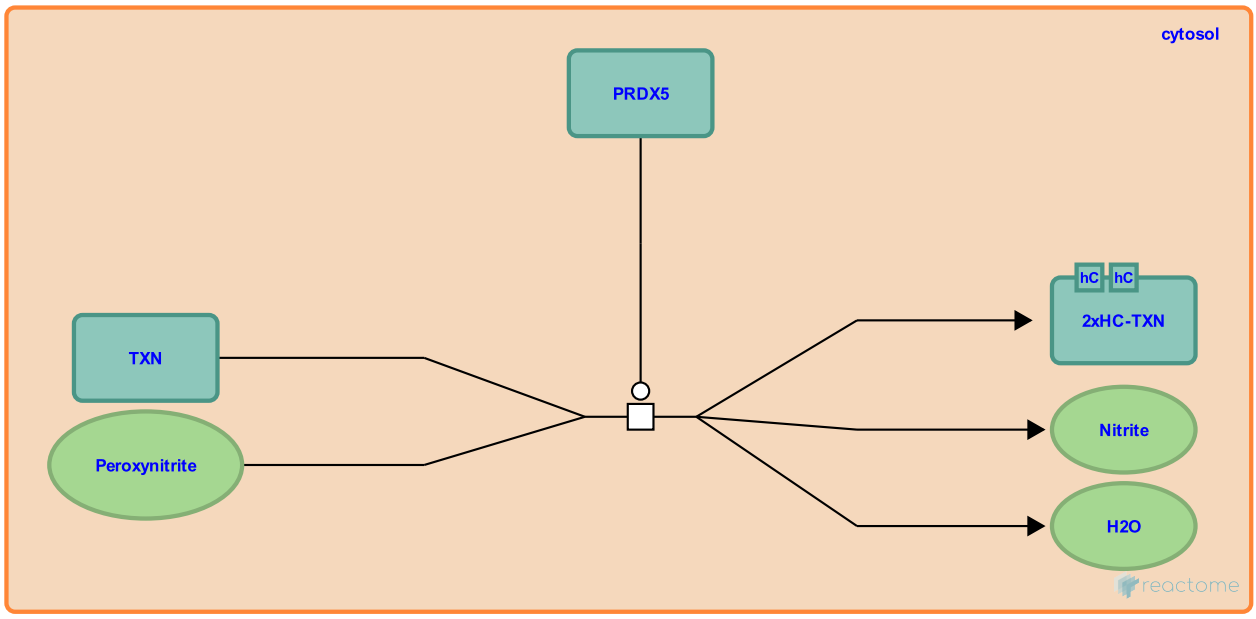
PRDX5 reduces peroxynitrite to nitrite using TXN ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3697882

Type: transition

Compartments: cytosol



Peroxiredoxin 5 (PRDX5) very efficiently reduces peroxynitrite using thioredoxin to yield nitrite (NO2-), water, and oxidized thioredoxin (Dubuisson et al. 2004). The N-terminal cysteine (Cys 47) of PRDX5 attacks the O-O peroxide bond of peroxynitrite.

Preceded by: Superoxide and nitric oxide react to peroxynitrite, thioredoxin, oxidized + NADPH + H+ => thioredoxin, reduced + NADP+

Literature references

Dubuisson, M., Vander Stricht, D., Clippe, A., Etienne, F., Nauser, T., Kissner, R. et al. (2004). Human peroxiredoxin 5 is a peroxynitrite reductase. *FEBS Lett., 571*, 161-5. ↗

Editions

2013-06-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

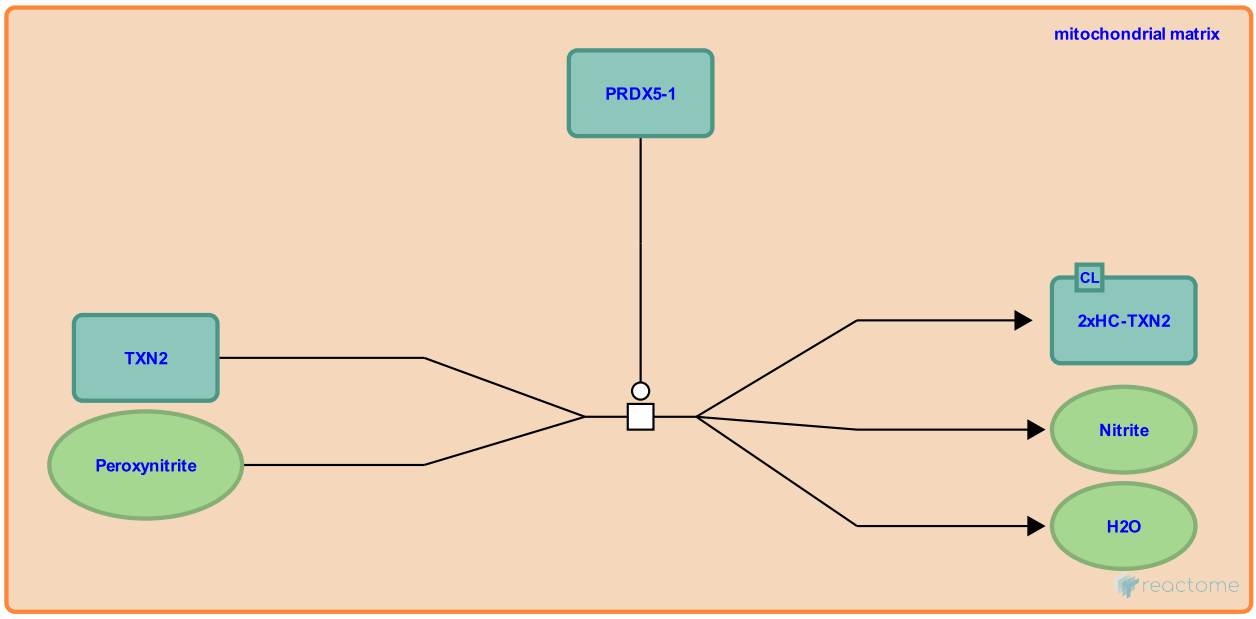
PRDX5 reduces peroxynitrite to nitrite using TXN2 ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3697894

Type: transition

Compartments: mitochondrial matrix



Peroxiredoxin 5 (PRDX5) very efficiently reduces peroxynitrite using TXN2 in mitochodria to yield nitrite (NO2-), water, and oxidized TXN2 (Dubuisson et al. 2004). The N-terminal cysteine (Cys 47) of PRDX5 attacks the O-O peroxide bond of peroxynitrite.

Preceded by: Superoxide and nitric oxide react to form peroxynitrite in mitochondria, TXNRD2 catalyzes the reduction of TXN2 by NADPH

Literature references

Dubuisson, M., Vander Stricht, D., Clippe, A., Etienne, F., Nauser, T., Kissner, R. et al. (2004). Human peroxiredoxin 5 is a peroxynitrite reductase. *FEBS Lett., 571*, 161-5. ↗

Radi, R., Cassina, A., Hodara, R., Quijano, C., Castro, L. (2002). Peroxynitrite reactions and formation in mitochondria. *Free Radic. Biol. Med., 33*, 1451-64. ↗

Editions

2013-06-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

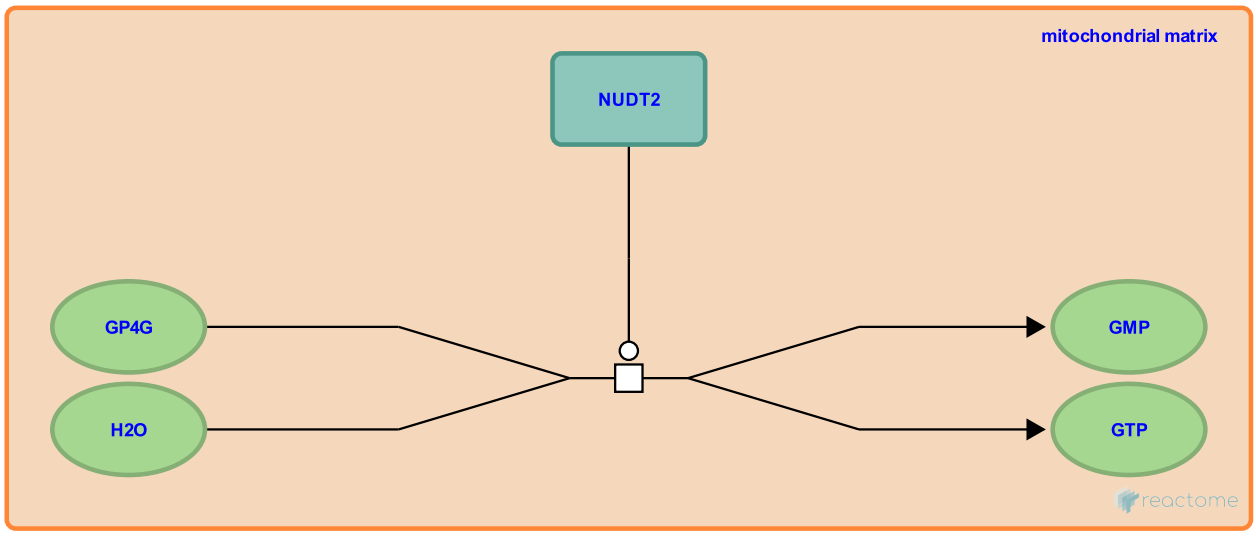
NUDT2 hydrolyses GP4G to GTP, GMP ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-5696197

Type: transition

Compartments: mitochondrial matrix



Bis(5'-nucleosyl)-tetraphosphatase (asymmetrical) (NUDT2) mediates the asymmetrical hydrolysis of P(1),P(4)-bis(5'-guanosyl) tetraphosphate (GP4G) to yield AMP and ATP. GP4G is implicated in the regulation of cellular responses to stress and its hydrolysis could serve as a mechanism by which homeostasis is maintained by preventing its build-up (Thorne et al. 1995, Swarbrick et al. 2005).

Literature references

Thorne, NM., Hankin, S., Wilkinson, MC., Nuñez, C., Barraclough, R., McLennan, AG. (1995). Human diadenosine 5',5'''-P1,P4-tetraphosphate pyrophosphohydrolase is a member of the MutT family of nucleotide pyrophosphatases. *Biochem. J., 311*, 717-21. ↗

Swarbrick, JD., Buyya, S., Gunawardana, D., Gayler, KR., McLennan, AG., Gooley, PR. (2005). Structure and substrate-binding mechanism of human Ap4A hydrolase. *J. Biol. Chem., 280*, 8471-81. ↗

Editions

2015-05-28	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

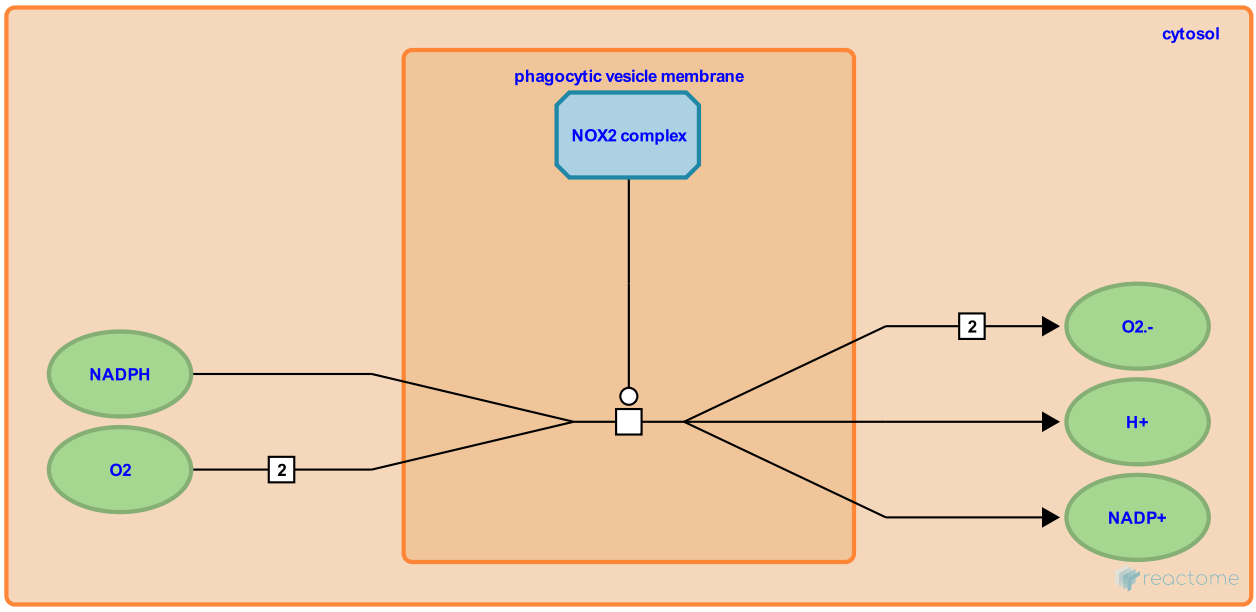
NOX2 generates superoxide from oxygen ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-1222376

Type: transition

Compartments: phagocytic vesicle membrane, cytosol



Macrophage NOX2 is a membrane complex that generates superoxide anions by reduction of oxygen with NADPH (Babior 1999, Dinauer et al. 1991).

Followed by: Superoxide and nitric oxide react to peroxynitrite

Literature references

Babior, BM. (1999). NADPH oxidase: an update. *Blood, 93*, 1464-76. ↗

Dinauer, MC., Pierce, EA., Erickson, RW., Muhlebach, TJ., Messner, H., Orkin, SH. et al. (1991). Point mutation in the cytoplasmic domain of the neutrophil p22-phox cytochrome b subunit is associated with a nonfunctional NADPH oxidase and chronic granulomatous disease. *Proc Natl Acad Sci U S A, 88*, 11231-5. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

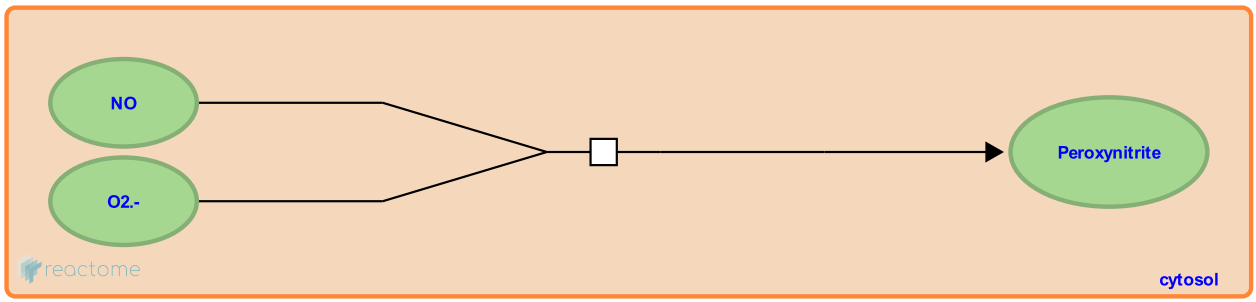
Superoxide and nitric oxide react to peroxynitrite ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-1222407

Type: transition

Compartments: cytosol



Nitric oxide and superoxide rapidly combine to form peroxynitrite (Pryor & Squadrito 1995).

Preceded by: NOX2 generates superoxide from oxygen

Followed by: PRDX5 reduces peroxynitrite to nitrite using TXN

Literature references

Pryor, WA., Squadrito, GL. (1995). The chemistry of peroxynitrite: a product from the reaction of nitric oxide with superoxide. *Am J Physiol, 268*, L699-722. ↗

Huie, RE., Padmaja, S. (1993). The reaction of no with superoxide. *Free Radic. Res. Commun., 18*, 195-9. ↗

Zielonka, J., Sikora, A., Joseph, J., Kalyanaraman, B. (2010). Peroxynitrite is the major species formed from different flux ratios of co-generated nitric oxide and superoxide: direct reaction with boronate-based fluorescent probe. *J. Biol. Chem., 285*, 14210-6. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

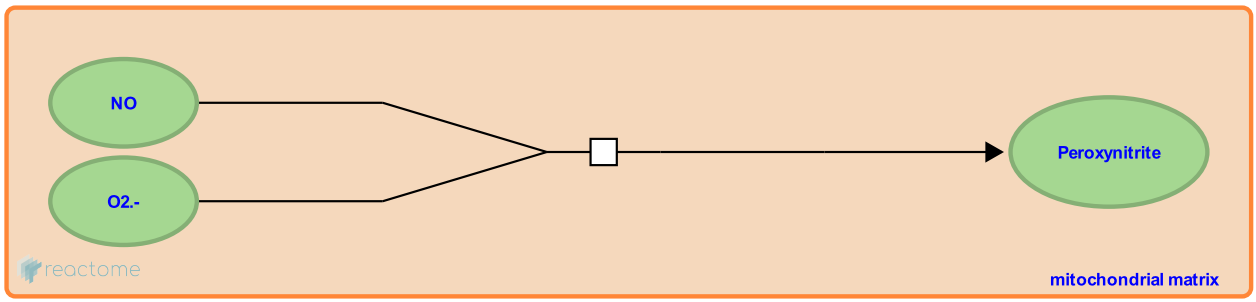
Superoxide and nitric oxide react to form peroxynitrite in mitochondria ↗

Location: Detoxification of Reactive Oxygen Species

Stable identifier: R-HSA-3697855

Type: transition

Compartments: mitochondrial matrix



Superoxide and nitric oxide react to form peroxynitrite within mitochondria (Huie and Padmaja 1993, Packer et al. 1996, reviewed in Radi et al. 2002).

Followed by: PRDX5 reduces peroxynitrite to nitrite using TXN2

Literature references

Radi, R., Cassina, A., Hodara, R., Quijano, C., Castro, L. (2002). Peroxynitrite reactions and formation in mitochondria. *Free Radic. Biol. Med., 33*, 1451-64. ↗

Huie, RE., Padmaja, S. (1993). The reaction of no with superoxide. *Free Radic. Res. Commun., 18*, 195-9. ↗

Zielonka, J., Sikora, A., Joseph, J., Kalyanaraman, B. (2010). Peroxynitrite is the major species formed from different flux ratios of co-generated nitric oxide and superoxide: direct reaction with boronate-based fluorescent probe. *J. Biol. Chem., 285*, 14210-6. ↗

Packer, MA., Porteous, CM., Murphy, MP. (1996). Superoxide production by mitochondria in the presence of nitric oxide forms peroxynitrite. *Biochem. Mol. Biol. Int., 40*, 527-34. ↗

Editions

2013-06-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

Table of Contents